

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Treatment for Hepatitis C Virus Infection in Adults*

Draft review available for public comment from February 23, 2012 to March 23, 2012.

Research Review Citation: Chou R, Hartung D, Rahman B, Wasson N, Cottrell E, Fu R. Treatment for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review No. 76. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 12(13)-EHC113-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Genentech, Public Reviewer	0. General	Consider including scientifically valid cohort studies. As stated on Page 8, the CER included randomized trials for all key questions. However, it only included cohort studies for Question 4 on harms or drug safety. For future reviews and technology assessments, we recommend the AHRQ consider including scientifically valid cohort studies in analyses of effectiveness to address questions such as Questions 1, 2 and 3 in this report. Consideration of well-designed and conducted cohort or observational studies is important, especially for subgroup analyses.	Thank you for the comment. The inclusion criteria (including which types of studies to include with each question) were developed in consultation with Key Informants, Technical Experts, and AHRQ. The risk of confounding in cohort studies of treatment benefits is considered to be high in the case of HCV infection and the Key Informants and Technical Experts recommended excluding them..
Genentech, Public Reviewer	0. General	Specify genotype when discussing dual therapy. We recommend that the CER specify genotype on a consistent basis when discussing trials about dual therapy. For example, on Page 17, the last paragraph discusses nine trials that compared dual therapies (citation numbers 20-23, 48-52). Further down in this paragraph, more specific data is described including information about genotypes 1, 2 and 3. We believe that by setting the context early and specifying the applicable genotypes in each of the nine trials up front, the AHRQ will avoid confusion for providers and patients who will use this report.	We agree that specifying genotype is important, and we have done so when possible. We would direct the reviewer to Table 2 where we have broken genotypes down into subgroups. The paragraph referred to by the reviewer describes which genotypes were included in which trials: "Three trials, including the trial that compared triple therapy regimens, included only enrolled patients with genotype 1 HCV infection; the others enrolled either a mix of genotypes or a specific genotype other than genotype 1." Information regarding genotype is also included in Table 2 and further broken out in KQ 2b, which evaluates differences in subgroups defined by genotype. In addition we have revised the first bullet point for KQ 2a to be clear that these trials enrolled patients with genotype 1, 2, or 3 infection and also revised the first sentence of the results for KQ 2a (p 17) similarly.

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Vertex, Public Reviewer	0. General	<p>To ensure the AHRQ report reflects recommendations for the 'real world' use of HCV therapies, it is important that the report evaluates treatment regimens that are approved by the FDA</p> <p>AHRQ's stated goal for this report is to "help with individualized clinical decision-making regarding antiviral therapy for chronic HCV infection." [Cites CER draft, ES-2] To achieve this goal the report should reflect therapies used in accordance with the US Prescribing Information, as expected in clinical practice. However, the AHRQ report gives equal importance to data from telaprevir's Phase II (PROVE1 and PROVE2) trials and the Phase III (ADVANCE and ILLUMINATE) trials. Telaprevir is approved by the FDA for use in genotype 1 chronic HCV patients as part of a triple therapy with peg-interferon alfa and ribavirin for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peg-interferon alfa and ribavirin, depending on the patient's viral response and prior response status. Additionally, the telaprevir Phase III trials also used an FDA labeled regimen outlined in the product label. The regimens used in PROVE1 and PROVE2 trials emphasized in the AHRQ report did not use response guided therapy, omitted ribavirin, or used 12 weeks total duration of treatment, none of which are FDA approved or used in clinical practice. By emphasizing and comparing FDA approved regimens, AHRQ can reflect the real world treatment options available to patients and their physicians, rather than speaking to experimental regimens that are not FDA approved.</p>	<p>We agree that it is important to focus on regimens likely to be utilized in clinical practice. However, with new drugs such as the protease inhibitors, it is also important to understand the results of key trials so clinicians and policymakers can best understand optimal treatment regimens. We describe the FDA approved regimens in the Introduction (Table 1) and also describe in the Results when a regimen was a FDA approved regimen. We do not agree that equal emphasis was placed on trials that evaluated 12-week regimens or omitted ribavirin; in fact, the Summary points and conclusions are based on trials that evaluated fixed-duration 24-week regimens or evaluated dose-response guided therapy.</p>

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Vertex, Public Reviewer	0. General	<p>Another point of concern is the seemingly inconsistent ratings of various trials throughout the report and evidence tables. AHRQ found the Phase III trial that compared the telaprevir dosing that was ultimately approved by FDA to dual therapy to be of “Good” (“quality”) rating, with clear blinding procedures, clear randomization methods, and clear reporting of attrition. It is unclear, then, why the same trial received a “Low” rating on “strength of evidence” on Key Questions 2a and 2b. For internal consistency of the report, we encourage AHRQ to consider revising the rating of the Jacobson trial based on the strength of the evidence criteria. It is not clear what criteria this trial did not meet based on AHRQ’s rating process.</p>	<p>Consistent with AHRQ’s methods guide for comparative effectiveness reviews we have assessed both individual study quality, and the strength of the body of evidence. Our approach is described in the Methods section, the grading of a body of evidence is based not solely on the quality of the individual studies, but also on other factors including the number and size of studies, consistency of results between studies, and directness of the evidence linking the intervention and health outcomes. In general, when there is only a single trial, it is difficult to draw a conclusion regarding the strength of the body of evidence.</p> <p>For further information we would direct the reviewer to the AHRQ methods guide on the EHC website, specifically to Chapter 10 - Grading the Strength of a Body of Evidence When Comparing Medical Interventions:</p> <p>AHRQ. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2011. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/122/328/2009_0805_grading.pdf</p>
Vertex, Public Reviewer	0. General	<p>Vertex encourages further consideration of the key evidence regarding the relationship between sustained virologic response (SVR) and clinical outcomes in the final AHRQ report.</p> <p>As the treatments for HCV continue to be investigated, the body of evidence demonstrating the efficacy of these treatments is growing. This is especially relevant with the advent of triple therapy regimens which demonstrate a higher likelihood of achieving SVR (63 percent to 75 percent for dual therapy with boceprevir and 75 percent to 80 percent for dual therapy with telaprevir). Moreover, the triple therapy evidence shows efficacy with a shorter total duration of treatment, 24 or 28 weeks, in some patients with early virologic response, compared with 48 weeks for dual therapy.</p> <p>As AHRQ noted, 16 cohort studies have found SVR associated with a reduced risk of all-cause mortality,</p>	<p>Thank you for the comment. We reviewed 19 cohort studies on the association between SVR and clinical outcomes in detail for KQ 4. We believe it is important to note potential issues regarding applicability (such as the potential differences between Asian and U.S. population). We appreciate the reviewer’s comment, and we have added a sentence to the Applicability section stating, “However, evidence showing that incidence of hepatocellular cancer is increasing in the U.S. in HCV-infected persons may attenuate such concerns regarding applicability.”</p>

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		<p>liver-related mortality, and other hepatic complications compared to populations that did not achieve SVR. [Cites CER draft, ES-11] Although each study had methodological concerns, we think it is worth nothing that their findings all trended in favor of SVR being associated with beneficial longer term outcomes. And while AHRQ noted that nine of the sixteen studies were conducted in Asia, interpreting this as a limitation of their generalizability, we believe that differences between the US and Asian populations may be representative of temporal rather than biological differences. Specifically, there is now a similar trend of increasing incidence of hepatocellular carcinoma (HCC) in the United States; in fact, it is the fastest rising cause of cancer related deaths in the US is likely due to HCV infection. Given that HCV-related complications, such as cirrhosis, liver cancer and liver failure often take decades to present, it is anticipated that a significant increase in these HCV-related morbidities and mortality will be seen as the baby boomer population ages as those who carry HCV infection will have been infected for decades. As such, we believe these studies conducted in Asia suggest where the US population may be in 20 or so years and believe these studies only further support the well-established relationship between SVR and clinical outcomes.</p>	

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Vertex, Public Reviewer	0. General	<p>To ensure clarity and reader expectation, we encourage AHRQ to more clearly state at the outset of the report that the patient population being assessed is treatment-naïve. Furthermore, as the report will influence the U.S. Preventive Services Task Force's (USPSTF) recommendations on screening, it is important that AHRQ clearly identify the patient population, so that there is no confusion for whom these recommendations were intended or how they should be applied.</p> <p>Additionally, it would be important to fully characterize the side effects mentioned in the report, such as "severe rash"; a clear and complete description of side effects is crucial to accurately compare the side effects of various treatments.</p>	<p>The first line of the Abstract (Objectives) states that the report pertains to treatment-naïve adults. This is reiterated in the Introduction (ES-2) and in the Methods and Discussion sections.</p> <p>Regarding harms of therapy, these are discussed in detail in KQ 3, including risk of severe rash (we report rates of rash overall, severe rash, and withdrawals due to adverse events, among others).</p>
Vertex, Public Reviewer	0. General	<p>Furthermore, while the AHRQ report assesses the benefits and harms of HCV treatment, it is important to also consider the harms associated with not treating HCV. The harms associated with not treating include patients advancing to cirrhosis and liver failure, use of the scarce resource of livers for transplantation, a reduced life expectancy, reduced quality of life, high treatment costs, and eventually death. Given the evidence that successful treatment and virologic cure has been shown to significantly reduce patient risk of death due to liver decompensation and liver cancer, we encourage AHRQ to consider this evidence in the final report.</p>	<p>The report describes the burden and clinical outcomes associated with HCV infection in the Introduction, and the harms associated with no treatment. Because no trials have compared current antiviral regimens to no treatment, it is not possible to directly assess harms of treatment versus no treatment; if such trials were available the harms of not treating would be the inverse of the benefits of treating (e.g., if the RR of treatment vs. no treatment was 0.5 for liver cancer, the RR of no treatment vs. treatment would be 2.0)..</p>
National Viral Hepatitis Roundtable (NVHR), Public Reviewer	0.1 General	<p>The current Draft Comparative Effectiveness Review, Hepatitis C Virus Infection Treatment in Adults, shows compelling evidence that the next set of guidelines should support a strong recommendation for screening and treatment of HCV. While the draft review acknowledged some of the challenges in assessing long-term outcomes due to the slow progression of liver disease, the available evidence is sufficient to establish the benefits of treatment, and hence the value of screening.</p>	<p>Thank you for the comment. The role of this report is to present the available evidence reported in published literature so that decisionmakers can make informed decisions about care. Decisionmakers may include guideline developers, healthcare providers, and patients. The role of the CER report is not to make recommendations regarding HCV screening, though other groups may do so.</p>

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National Viral Hepatitis Roundtable (NVHR), Public Reviewer	0.2 General	The protease inhibitors that the FDA approved in 2011 can arrest this virus. Protease inhibitors, when added to standard dual therapy, are associated with substantially higher sustained virologic response rates (SVR) and potentially shorter duration of therapy. The draft review cites new evidence demonstrating an association between achievement of SVR and reduced risk of all-cause mortality, supporting the validity of SVR as a surrogate endpoint in HCV. These recent developments in antiviral therapies will have a strong impact on the real-world effectiveness of treatment for those who have been diagnosed with chronic HCV infection.	We appreciate your comment; please see response to similar comment above.
National Viral Hepatitis Roundtable (NVHR), Public Reviewer	0.3 General	Given the evidence, coupled with the robust research landscape aimed at developing even more effective interferon-free HCV treatment regimens in the near future, the National Viral Hepatitis Roundtable calls on AHRQ and USPSTF to support a public health agenda to eliminate the hepatitis C epidemic. USPSTF recommendations guide clinical practice and reimbursement; without supportive guidelines from the USPSTF, hundreds of thousands of patients will be at significant risk for disease progression and death.	We appreciate your comment. This report presents the available evidence. The USPSTF will use this report in their deliberations about Hepatitis C screening
National Viral Hepatitis Roundtable (NVHR), Public Reviewer	0.4 General	The draft review notes that the USPSTF will consider this treatment review together with its screening review in its update, providing a basis and rationale for USPSTF to change its current HCV screening recommendations. As patient advocates, we see a clear and logical association between testing, treatment, and clinical outcomes: patients can't be treated unless they have been diagnosed, and patients who are diagnosed late or not at all face substantial morbidity and mortality – risks which can be significantly reduced by successful treatment.	We appreciate your comment, thank you for sharing the perspective of the National Viral Hepatitis Roundtable. We appreciate your commitment to individuals with hepatitis

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Peer Reviewer 1	1. General Comments	<p>This is a well written and comprehensive review of the literature comparing the effectiveness of various strategies in treating treatment-naive chronic hepatitis C. Specifically compared are interferon alpha 2a and interferon alpha 2b as part of combination therapy with ribavirin; varying doses and durations of antiviral therapy and dual combination therapy to triple therapy including recently licensed protease inhibitors.</p> <p>The review is balanced and free of bias but the review limits itself to treatment-naive individuals and does not consider "difficult-to-treat" populations (e.g., HIV-coinfected, renal failure, major comorbidities, psychopathology, etc).</p>	<p>Thank you for taking the time to review this report in such detail. Your comments are greatly appreciated.</p> <p>After consultation with Key Informants, members of the Technical Expert Panel, and AHRQ medical officers, we limited the review to treatment-naïve individuals and did not include co-infected populations with HIV or persons with end-stage renal disease... As a clarification; we did not exclude patients with other comorbidities or psychopathology. It was thought that a review of antiviral treatments in treatment-naive patients was an important and large enough area to be covered in a CER, particularly given the new increasingly effective treatments available for this population. Treatment decisions for HIV-coinfected patients and persons with end-stage renal disease might differ from those in patients without these conditions; in addition, we are not aware of trials of antiviral treatments that have specifically enrolled patients with end-stage renal disease. Additional CERs of treatments in HIV-coinfected patients, patients with end-stage renal disease, and patients who have failed previous antiviral treatments may certainly be warranted; however, inclusion of those populations would have substantially increased the scope and resources required for this CER and would have resulted in a less-focused report. We have included the rationale for our exclusion in the methods section of the report.</p>
Peer Reviewer 2	1. General Comments	The report is very clinically meaningful. The key questions are appropriate and explicit. The target population and audience are both well defined.	Thank you. Your feedback is appreciated.

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Peer Reviewer 5	1. General Comments	<p>The prevalence of HCV in the US is considered to be as high as 6 M for antibodies, 5 M for HCV RNA positive. This manuscript and others need to list at least 10 references and describe and explain the wide range of prevalence data.</p> <p>one of many references Hepatitis C virus infection in USA: an estimate of true prevalence Eric Chak, Andrew H. Talal, Kenneth E. Sherman, Eugene R. Schiff and Sammy Saab</p>	<p>The article cited by the reviewer does not report actual seroprevalence survey data; rather it is essentially a modeling study using varying sources to estimate the prevalence of HCV infection. Therefore we did not add it as a citation in the Introduction. We believe that the NHANES data cited in the background of the report is the most accepted and accurate estimate, and actually fairly close to the Chak study estimate (1.6% vs. 2.0%). In the report, we clarified that NHANES is based on a national household survey. The purpose of the background is not to provide a detailed discussion and comprehensive citations on the prevalence of HCV infection and reasons for relatively mild differences in prevalence estimates; rather we discuss and cite key references that provide context for the importance of the report</p>
Peer Reviewer 6	1. General Comments	<p>Generally it is a very good article that outlines very distinctly what its goals are. The plan on how those goals were achieved were described fully. The key questions were well stated and thus easy to follow how they were answered.</p>	<p>Thank you for your comment.</p>
Peer Reviewer 6	1. General Comments	<p>We have reviewed this draft report, and did not come across any major inconsistencies in reporting or translational challenges. The report is well-written, and might support clinical decisionmaking in Hepatitis C treatment, and have an additional impact on Hepatitis C screening practices.</p>	<p>Thank you for taking the time to review this report. Your feedback is appreciated.</p>
Richard Chapell for Merck & Co., Inc, Public Reviewer	1. Structured Abstract	<p>The difference in SVR rates between interferons 2a and 2b is given as 6%. Elsewhere in the review this number is given as 8% or 7.8%. Please ensure that the figure quoted is accurate and is consistent throughout the review. As will be discussed below, the abstract states that boceprevir is associated with increased risk of hematological adverse events without mentioning that Telaprevir is also associated with such events. This is in contrast to Telaprevir's association with dermatological adverse events, which are unique to this drug and not shared by Boceprevir. Please revise to reflect an accurate assessment of adverse event rates.</p>	<p>Thank you for pointing this out, we have made the necessary corrections. The figure of 8% was simply rounded up from 7.8%. The figure of 6% was an error.</p> <p>Throughout the report we have corrected the reported absolute difference and made sure it was reported accurately and consistently. We have made distinctions in our report regarding the adverse events for each drug.</p>

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Peer Reviewer 4	1.1 General Comments	<p>The team has done a remarkable job at collating all relevant data in an attempt to make sense of the rapidly expanding literature in this report. This was a difficult task and is done very well.</p> <p>Is the report clinically meaningful: Yes and no.</p> <p>I think that the analysis is meaningful in regards to patients with genotype 2 and 3 HCV, where there are enough data to allow comparisons across the available agents, their duration, and dose. The results are also meaningful for some of the subgroup analyses presented in the report (such as those in patients with high versus low viral load undergoing triple therapy). This is not the case with most of the data pertaining to the most common genotype 1 HCV.</p>	<p>Thank you for the comments. We evaluated the available evidence on effectiveness in subgroups in the trials of triple therapy vs. dual therapy in patients with genotype 1 infection (see KQ 2b). Although data are somewhat limited, we believe there was moderate evidence to reach some conclusions about no difference in relative efficacy for race or sex, though there appeared to be differences for high versus low viral load (see KQ 2b). We agree with the reviewer that additional data related to subgroups defined by age and baseline fibrosis stage are limited at this time, and added this to the Limitations of the Evidence Base section: "Fourth, there was relatively limited information on effects of newer triple therapy regimens with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors. Such information would be helpful for individualizing treatment decisions with these regimens."</p>
Genentech, Public Reviewer	1.1a Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	<p>Clarify statements regarding the sustained virologic response (SVR) observed for dual therapy with pegylated interferon alfa-2a and pegylated interferon alfa-2b: In several places throughout the draft CER, statements regarding the SVR for pegylated interferon alfa-2a and pegylated interferon alfa-2b are inconsistent, and reported numeric values vary.</p>	<p>Thank you for your comment. We have revised this analysis, excluding an additional trial comparing alfa-2a and alfa-2b in the context of triple therapy with telaprevir (Marcellin et al.). We have edited to report to reflect these changes</p> <p>We have revised this for consistency.</p> <p>Revised for consistency to 9% absolute difference (95% CI 2% - 15%).</p>
Genentech, Public Reviewer	1.1b Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	<p>More specifically, the draft CER mistakenly states that the SVR for dual therapy with pegylated interferon alfa-2b plus ribavirin is higher than for pegylated interferon alfa-2a plus ribavirin (Pages ES-20 and 69-70), however elsewhere, pegylated interferon alfa-2b is reported to achieve a lower SVR than pegylated interferon alfa-2a (Pages v, ES-7, ES-10, ES-20, 2, 15, 20, 59, and 68).</p>	<p>Thank you for your comment. We have revised for consistency to 9% absolute difference (95% CI 2% - 15%).</p> <p>Revised for consistency to 9% absolute difference (95% CI 2% - 15%).</p> <p>Changed to revised estimate 0.86 (0.78 - 0.95).</p>

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<p>Genentech, Public Reviewer</p>	<p>1.1c Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)</p>	<p>We recommend that the AHRQ clarify statements about the SVR differences between alfa-2a and alfa-2b, correct the absolute difference in SVR rates to a consistent numerical value, and specify the genotype(s) relevant to the data in a consistent way.</p> <p>(p.v.): In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower for dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 6 percentage points.</p> <p>(ES-7): In trials of treatment-naïve patients, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a slightly lower likelihood of achieving an SVR compared with dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 8 percentage points.</p> <p>ES-10): In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.90, 95% CI 0.84 to 0.96), with a difference in absolute SVR rates of about seven percentage points.</p> <p>(ES-20):For patients with genotype 2 or 3 infection, dual therapy with pegylated interferon alfa-2b plus ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2a plus ribavirin, but absolute differences were relatively small.</p>	<p>Thank you for your comment. We have changed to: "dual therapy with pegylated interferon alfa-2a plus ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2b plus ribavirin, but absolute differences were relatively small."</p>

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Peer Reviewer 4	1.2 General Comments	<p>With the availability of new antiviral agents (and clinical trials showing that treatment regimens including these agents to previous standard is clearly superior in terms of efficacy), the standard of care for antiviral treatment has changed from dual to triple therapy. Thus, the most relevant question is the comparative effectiveness of the 2 new DAA—of the 2 available regimens, which triple therapy may be better than the other. The problem is that with the rapidly expanding field, by the time there are enough data to address this question; we will probably have newer and perhaps better agents to include in the mix. Although recognized by the authors, this limitation of the evidence base limits the applicability of the current review to the majority of patients with HCV in the U.S.</p> <p>Are the target population and audience explicitly defined? Yes</p> <p>Are the key questions appropriate and explicitly stated? Yes</p>	<p>Thank you for your comments. We acknowledge that rapid changes in treatment options in this field of study, and to ensure the relevancy of the review we added the newer regimens when they were FDA approved. We made a statement to this effect in the Future Research section: "Trials directly comparing triple therapy with telaprevir compared with triple therapy with boceprevir would be very helpful for understanding comparative effectiveness of these two protease inhibitors." We also noted that other protease inhibitors and other newer drugs and regimen for HCV infection (including non-interferon-based regimens) are expected, but published data in treatment-naive patients are not yet available.</p>
Genentech, Public Reviewer	1.2a Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	(p.2): Although previous reviews found insufficient evidence to determine whether dual therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b is more effective, more head-to-head trials directly comparing these two regimens are now available.	<p>References fixed.</p> <p>Changed absolute SVR rate change to 8%.</p>
Genentech, Public Reviewer	1.2b Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	(p.15): Seven trials of patients with genotype 2 or 3 infection found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.88, 95% CI 0.81 to 0.96; I ² =37%), with an absolute difference in SVR rates of 7.8 percentage points (95% CI 2.2 to 13.4 percentage points).	<p>Thank you for your comment,, we have made the following changes:</p> <p>Changed absolute SVR rate change to 8%.</p> <p>Changed absolute SVR rate change to 8%.</p>

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Genentech, Public Reviewer	1.2c Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	<p>(p.20):Based on published trials that evaluated standard doses of pegylated interferon, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with slightly lower likelihood of achieving an SVR compared with pegylated interferon alfa-2a plus ribavirin (7 trials, pooled RR 0.88, 95% CI 0.81 to 0.96; I2=67%). The pooled absolute reduction in likelihood of SVR was 7.8 percentage points (95% CI 2.2 to 13 percentage points).</p> <p>(p.59):In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.90, 95% CI 0.84 to 0.96), with a difference in absolute SVR rates of about seven percentage points.</p>	Thank you for your comment, we have changed to: "dual therapy with pegylated interferon alfa-2a plus ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2b plus ribavirin, but absolute differences were relatively small."
Genentech, Public Reviewer	1.2d Structured Abstract (p.v); Executive Summary (ES-7, ES-10, ES-20); Introduction (p.2); Results (p. 15, 20, 59); Discussion (68, 69-70)	<p>(p.68): Our findings regarding the comparative effectiveness of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin are consistent with recent systematic reviews that also found the former associated with a lower likelihood of SVR.</p> <p>(p.69-70):For patients with genotype 2 or 3 infection, dual therapy with pegylated interferon alfa-2b plus ribavirin appears to be associated with higher likelihood of achieving SVR compared to dual therapy with pegylated interferon alfa-2a plus ribavirin, but absolute differences were relatively small.</p>	Thank you for your comment, please see above responses for similar comments
Genentech, Public Reviewer	2. Executive Summary	Correct errors in referring to pegylated interferon alfa-2a vs. alfa-2b. We recommend that the AHRQ recheck the report to ensure that it contains correct references to pegylated interferon alfa-2a vs. pegylated interferon alfa-2b. For example, on Page ES-13 last row and Page ES-14 third row from the bottom, "alfa-2b" should be "alfa-2a". Triple therapy with telaprevir was studied with pegylated interferon alfa-2a, not alfa-2b.	Corrected "summary of evidence table" in the Executive Summary so that telaprevir triple versus dual therapy regimens are reported as being with pegylated interferon alfa-2a.

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Vertex, Public Reviewer	2. Executive Summary (ES-1) and Introduction (p.1)	Vertex encourages AHRQ to consistently define SVR as "HCV RNA undetectable 24 weeks following completion of treatment," as defined on pg. 7 of the report.	SVR was defined in this way throughout the report.
Vertex, Public Reviewer	2. Executive Summary (ES-10)	The report states that "trials evaluating the boceprevir regimen recommended by the FDA for antiretroviral-naïve patients with cirrhosis reported SVR rates of 66% to 75%." This SVR rate applies to all patients, not just patients with cirrhosis.	Thank you for your feedback. The sentence states that these are results for the boceprevir regimen recommended by the FDA for antiretroviral-naïve patients with cirrhosis, which is accurate. While this SVR rate may apply to non-cirrhotic patients, the trials and the evidence we reviewed do not make that distinction for this specific treatment regimen, and so we cannot confidently state that the SVR rate applies to all patients.
Vertex, Public Reviewer	2. Executive Summary (ES-10, ES-11)	The term "antiretroviral" referenced in the report is a term pertinent for HIV medications and not for HCV treatment.	Thank you for your comment. We fixed the typo.
Richard Chapell for Merck & Co., Inc, Public Reviewer	2. Executive Summary (ES-12)	Row 1: "...slightly better short-term scores..." Please state whether the difference is statistically significant, and, if so, please state the magnitude of the difference and the p-value.	We revised this to indicate that differences were statistically significant. We did not add the magnitude of difference or the p values since there were many different quality of life measures reported and the values varied; the details are provided in the text for Key Question 1a.
Richard Chapell for Merck & Co., Inc, Public Reviewer	2. Executive Summary (ES-12)	Row 7: the reviewer speculates that heterogeneity may be the result of differences in ribavirin dosing. However, on page ES-13, row 3, it is reported that differences in ribavirin dosing had no effect of SVR. Please resolve this apparent contradiction.	We do not think there is any contradiction. For KQ 2a we performed a sensitivity analysis of pooled results, excluding a trial of dual therapy with pegylated interferon alfa-2a vs. dual therapy with pegylated interferon alfa-2b, and found no difference in the relative risk estimate compared to the analysis (though statistical heterogeneity was slightly reduced). The text on ES-13 identified by reviewer discusses the results of a separate set of three trials that directly compared effects of differential ribavirin dosing (with the same pegylated interferon regimen) and also found no clear effects on results.
Vertex, Public Reviewer	2. Executive Summary (ES-13) and Results (p.36, 37)	For purposes of clarity, Vertex encourages AHRQ to reference the studies it references in the evidence tables.	Thank you. We have added the references in our updated revision.
Richard Chapell for Merck & Co., Inc, Public Reviewer	2. Executive Summary (ES-17; ES-18)	ES-17, row 4 and ES-18, row 1: Triple therapy with Telaprevir was associated with increased risk of anemia. This increased risk goes unmentioned in several places in the document in which increased hematological adverse events with Boceprevir are noted. Please resolve this inconsistency.	Revised to state: "However, triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir and anemia and rash (including severe rash in <10% of patients that could result in treatment discontinuation) with telaprevir."

Commentator & Affiliation	Section	Comment	Response
Vertex, Public Reviewer	2. Executive Summary (ES-2)	Boceprevir has a duration of therapy of 28 weeks, as opposed to 24 weeks, as suggested in the report.	The duration of boceprevir was reported accurately. The total duration of treatment was 28 weeks—the regimens were described accurately as a 4-week run-in period of dual therapy followed by 24 weeks of triple therapy with boceprevir.
Vertex, Public Reviewer	2. Executive Summary (ES-21) and Introduction (p.2)	Current screening recommendations are based on a high-risk patient screening criteria, in addition to “the effectiveness of treatments in persons found to have HCV infection by screening.”	Thank you for the comment. The role of the CER report is not to make recommendations regarding HCV screening, though other groups may do so.
Richard Chapell for Merck & Co., Inc, Public Reviewer	2. Executive Summary (ES-7)	2nd sentence: Sentence structure is confusing. "Of the 1,177 citations identified at the title and abstract level, we screened and reviewed, 294 studies were selected for full-length articles." If we are interpreting the sentence correctly, it could be revised to state "Of the 1,177 citations identified, screened and reviewed at the title and abstract level, 294 studies were selected to be acquired as full-length articles."	Thank you for your suggestion, we have re-worded this statement to more clearly describe that the number of studies selected for full-text review, came from the larger number of citations that were identified at title and abstract level.
Vertex, Public Reviewer	2. Executive Summary (ES-7)	For purposes of clarity, Vertex encourages AHRQ to cite the trials it references in the report.	Thank you, we have cited all included trials in the report and listed them in our appendices within the included studies list and the evidence tables.
Richard Chapell for Merck & Co., Inc, Public Reviewer	2. Executive Summary (ES-8; ES-11; ES-20)	ES-8, paragraph 1; ES-11, paragraph 3; ES-20, paragraph 6: Again, the review states that Boceprevir is associated with increased risk of hematological adverse events without mentioning that Telaprevir is also associated with such events. Please revise to reflect an accurate assessment of adverse event rates. We will discuss the reasoning underlying this request below under "Discussion".	We revised to indicate at each appropriate location in text and tables that boceprevir and/or telaprevir were associated with hematological adverse events wherever applicable.
Vertex, Public Reviewer	2. Executive Summary (p.v,ES-7, ES-10)	The percentage difference in likelihood of achieving an SVR for treatment-naïve patients who experience dual therapy with pegylated interferon alfa-2b and ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin is stated differently throughout the report.	Thank you. We have reviewed the report and made changes accordingly.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	2. Introduction	<p>The introduction is accurate and reasonably appropriate.</p> <p>It would be appropriate to include risk factors for infection and emphasize the importance of parenteral drug abuse and the high prevalence of significant psychiatric comorbidity in this population. Generally, ongoing substance abuse and major psychiatric diagnoses are relatively strong contraindications to the use of interferon-containing antiviral regimens.</p>	<p>Thank you for your feedback. We describe risk factors in the first paragraph of the Introduction: "HCV is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use the strongest risk factor." Criteria for antiviral treatment eligibility have expanded over time, in part due to more effective therapies, and now patients may be treated even in circumstances of ongoing substance abuse or psychiatric diagnoses, as described in recent clinical practice guidelines. However, we discuss in the Applicability section that most of the trials could be considered efficacy studies because they excluded patients with common comorbidities (such as psychiatric conditions or recent or ongoing substance abuse) who may receive treatments in clinical practice.</p>
Peer Reviewer 2	2. Introduction	<p>The introduction is a brief but quite accurate and well written review of the hepatitis C problem in the United States. It is concise but complete and an excellent start to this paper.</p>	<p>Thank you.</p>
Peer Reviewer 4	2. Introduction	<p>The background section is brief and to the point. It is very clear and logical.</p>	<p>Thank you.</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	2. Introduction	<p>Line 17 page 12: the best predictor of response is the 4 week viral response on treatment this section should clearly denote: prior to treatment</p> <p>Line 46 page 12 Why is this review not including previous treatment nonresponders, relapse, null responders, partial responders</p>	<p>See response above regarding prevalence of HCV infection.</p> <p>Although early (4-week) virological response predicts SVR, SVR is a better predictor of long-term remission of HCV infection, as supported by the reference included on page 8 (reference 15) and other references. We state previously that early virological response predicts SVR.</p> <p>It was thought that a review of antiviral treatments in treatment-naïve patients was an important and large enough area to be covered in a CER, particularly given the new increasingly effective treatments available for this population. . Additional CERs of treatments in HIV-coinfected patients, patients with end-stage renal disease, and patients who have failed previous antiviral treatments may certainly be warranted; however, inclusion of those populations would have substantially increased the scope and resources required for this CER and would have resulted in a less-focused report. We discussed this with KI, TEP and AHRQ MO, and they affirmed this decision, we limited the review to treatment-naïve individuals and did not include co-infected populations. We discussed this with KI, TEP and AHRQ MO, and they affirmed this decision.”</p>
Peer Reviewer 6	2. Introduction	Did a very good job in introducing the topic and describing the plan on how it was going to be achieved. Also gave some good background on the problem.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Martha Saly, Public Reviewer	3. Introduction	The burgeoning hepatitis C epidemic poses a major public health crisis in the United States, with hepatitis C-associated deaths now exceeding annual mortality from HIV/AIDS, and steadily increasing. The 2010 Institute of Medicine report Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C documents the failure to address the hepatitis C epidemic through established measures and proven interventions. The National Viral Hepatitis Roundtable raised a number of concerns in our response to the recent the Draft Comparative Effectiveness Review, Screening for Hepatitis C Virus Infection in Adults. The current Draft Comparative Effectiveness Review, Hepatitis C Virus Infection Treatment in Adults, shows compelling evidence that the next set of guidelines should support a strong recommendation for screening and treatment of HCV. While the draft review acknowledged some of the challenges in assessing long-term outcomes due to the slow progression of liver disease, the available evidence is sufficient to establish the benefits of treatment, and hence the value of screening.	Thank you for your helpful comments and feedback.
Richard Chapell for Merck & Co., Inc, Public Reviewer	3. Introduction	The review is limited to treatment-naïve patients, even though patients for whom dual therapy has failed are a large portion of the hepatitis C population. Please include language to justify this limitation. If the reason is that the report is considered a supplement to the concurrent report on hepatitis C screening and thus only addresses patients identified by screening, please make this explicit.	Thank you for your comment. It was thought that a review of antiviral treatments in treatment-naive patients was an important and large enough area to be covered in a CER, particularly given the new increasingly effective treatments available for this population. Additional CERs of treatments in patients who have failed previous antiviral treatments may certainly be warranted; however, inclusion of those populations would have substantially increased the scope and resources required for this CER and would have resulted in a less focused report. We discussed this with KI, TEP and AHRQ MO, and they affirmed this decision
Genentech, Public Reviewer	3. Introduction (p.3)	Consider adding dosing recommendation for boceprevir. On Page 3, Table 1 describes the pharmacokinetics, indications and dosing of included drugs. The dosing recommendations are included for all drugs except for boceprevir. For completeness, we recommend that for completeness, the AHRQ add the dosing information for boceprevir.	Thank you. We have added boceprevir dosing to Table 1.

Commentator & Affiliation	Section	Comment	Response
Genentech, Public Reviewer	3. Introduction (p.3)	Revise notation that boceprevir was tested exclusively with pegylated interferon alfa-2b. On Page 3, Footnote "a" states that "boceprevir was tested exclusively with pegylated interferon alfa-2b and that telaprevir primarily with pegylated interferon alfa-2a"; however, this statement may be misleading without additional context. In the FDA-approved label, boceprevir's pivotal studies involved alfa-2b only, and telaprevir's pivotal studies involved alfa-2a only. On the other hand, beyond the label-enabling trials, both antivirals have been studied to some extent with alfa-2a and alfa-2b. Specifically, boceprevir has been studied with alfa-2a,3 although this study was conducted in patients who have been previously treated whereas the target population of this CER is treatment-naïve patients. We recommend that the AHRQ clarify the intent and context of this statement.	Thank you for your note, we have revised the footnote to Table 1 to state: "The manufacturer packaging and dosage information does not specify a particular pegylated interferon (alfa-2a or -2b) for either drug, though in trials conducted to obtain FDA approval, boceprevir was tested with pegylated interferon alfa-2b and telaprevir with pegylated interferon alfa-2a."
Vertex, Public Reviewer	3. Introduction (p.3)	Table 1, which references pharmacokinetics, indications, and dosing of included drugs, does not list studies on patients who have been treated for HCV.	We are not sure what the reviewer is referring to here. The Table is intended to describe the pharmacokinetics, indications, and dosing of included drugs, not provide a list of studies of different antiviral treatments.
Peer Reviewer 1	3. Methods	The search strategy appears appropriate.	Thank you.
Peer Reviewer 2	3. Methods	The search strategies are quite logical and well defined. The definitions are appropriate as are the statistical methods used. Both the inclusion and exclusion criteria are justifiable and well stated.	Thank you. We made an effort to be as explicit in our criterion and methodology as possible.
Peer Reviewer 4	3. Methods	I have no reservations in regards to the inclusion / exclusion criteria, search strategies, or outcomes measures. The statistical methods are generally sound. My main reservation is related to the analysis for key question 2: I think that the results should be stratified based on HCV genotype. Combining studies with only genotype 1 patients to studies with other genotypes may not be the best strategy. In practice, we know whether a patient is genotype 1 or non-1, and the results are presented may not be directly applicable to the patient seen in clinical practice.	For KQ 2a, genotypes 1, 2, and 3 were only reported together for comparisons of dual therapy with pegylated interferon alfa-2a vs. dual therapy with pegylated interferon alfa-2b. KQ 2b reported results of trials that stratified results by HCV genotype, which showed no clear differences in likelihood of achieving an SVR. For all other parts of KQ 2, results were stratified by genotype 1 and genotype 2/3. Genotypes 2 and 3 are thought to respond similarly to antiviral treatments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	3.2 Methods	<p>I do not think that the study by Marcellin et al (reference 51) belongs in the group evaluating the comparative effectiveness of dual therapy with peginterferon alfa-2a vs. alfa-2b. Recommend removing this from the primary analysis – may consider adding in as a sensitivity analysis</p> <p>Also, I am not sure if I would undermine the importance of IDEAL trial on the basis of different ribavirin doses used across the 2 peginterferon groups. If anything, ribavirin exposure was lower in patients who received peginterferon alfa-2b in IDEAL study. “Correcting” for the ribavirin dose might make peginterferon alfa-2b more effective than alfa-2a – pushing the overall estimate from this meta-analysis towards null.</p>	<p>Thank you for your suggestion, we have removed the Marcellin trial from the main analysis since it was strictly speaking not dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b (it was triple therapy with pegylated interferon alfa-2a versus triple therapy with pegylated interferon alfa-2b). This had no effect on the estimate. We did include the Marcellin trial in a sensitivity analysis.</p> <p>IDEAL was included in the main analysis of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b. However, ribavirin dosing was complicated in the IDEAL trial and could be higher or lower with pegylated interferon alfa-2b compared to pegylated interferon alfa-2a depending on body weight. Therefore, we think it was appropriate to perform a sensitivity analysis that excluded IDEAL; the estimate was very similar.</p>
Peer Reviewer 5	3. Methods	<p>Are the inclusion and exclusion criteria justifiable? Yes, although I am not sure why nonresponder and relapse data is not part of this survey</p> <p>Are the search strategies explicitly stated and logical? Yes</p> <p>Are the definitions or diagnostic criteria for the outcome measures appropriate? Yes</p> <p>Are the statistical methods used appropriate? agree</p>	Thank you for your comment, please see response to similar comment above
Peer Reviewer 6	3. Methods	This was a systematic review so the search strategy is an important piece of the article. The EPC has a long track record of doing similar reviews and is very well versed in the literature and doing these types of reviews.	Thank you.
Vertex, Public Reviewer	4. Methods (p.14)	Under Key Question 1a, the definition of “current antiviral treatment regimens for chronic HCV infection” is not current standard of care, which includes triple therapy regimens.	Dual therapy with pegylated interferon plus ribavirin remains the current standard for treatment of genotypes 2 or 3 infection, so we believe this statement remains accurate.
Vertex, Public Reviewer	4. Methods (p.14) and Results (p.35, 36, 37)	For purposes of clarity, Vertex encourages AHRQ to ensure that the references refer to the studies being addressed.	Thank you for your comment, please see response to similar comment above

Commentator & Affiliation	Section	Comment	Response
Richard Chapell for Merck & Co., Inc, Public Reviewer	4. Methods (p.8)	"We did not evaluate improvement in liver function tests as an intermediate outcome (e.g., sustained biochemical response, or normalization of liver transaminases six months after the end of a course of therapy), due to its poor correlation with SVR." and " Because many factors (such as age, race, viral load, and fibrosis stage) may be associated with both the likelihood of achieving an SVR as well as the likelihood of hepatic complications..." Please provide a reference in support of these statements.	We added these references: Civeira MP et al. J Hepatology 1999;31 (Suppl 1):S237-S243; Hung CH et al. J Gastroenterol Hepatol 2002;17:130711; Zeuzem S et al. N Engl J Med 2000;343:1666-72; Basso M et al. Hepatology 2009;49:1442-8.
Peer Reviewer 1	4. Results	Studies are well summarized. It may be appropriate to point out that many of the large multicenter studies referenced are, in fact, conceived, planned and funded by pharmaceutical sponsors.	Thank you. We reported funding sources for all included studies in our evidence tables shown in Appendix G, but did not call this out in the Results section of the report in an effort to maintain objectivity for the reader. We have added this to the Discussion/Limitations of the Evidence Base section of the report.
Peer Reviewer 2	4. Results	The results section is also well written and contains the appropriate detail needed. The characteristics of the study are clearly defined and the key messages are quite applicable. I do not feel that the investigators overlooked any studies that should have been included nor did they include studies that ought to have been excluded. The figures, tables and appendices are more than adequate and supportive of the results section.	Thank you. We made every effort to include relevant and supportive figures and tables wherever possible.
Peer Reviewer 4	4. Results	Is the amount of detail presented in the results section appropriate? Yes Are the characteristics of the studies clearly described? Yes Are figures, tables and appendices adequate and descriptive? Yes Did the investigators overlook any studies that ought to have been included or conversely did they include studies that ought to have been excluded? Are the key messages explicit and applicable? : I addressed some of my concerns in the section above.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	4. Results	<p>line 41 page 29 I find the text here confusing: at an earlier point in the manuscript it is stated that SVR with Peg a2a is equal to a2B, here it is stated it is lower. There is a need to make sure there is consistency in the text relative to this issue.</p> <p>page 105 described a2b as better than a2a for genotype 2,3</p>	<p>This section does not compare dual therapy with pegylated interferon alfa-2b versus -2a; it compares dose effects of pegylated interferon alfa-2a or -2b as part of dual therapy. The results are accurate and state: "Lower dose pegylated interferon alfa-2a as part of dual therapy with ribavirin was associated with decreased likelihood of achieving an SVR compared with standard dose (five trials, pooled RR 0.86, 95% CI 0.76 to 0.98)."</p> <p>We found no reference to pegylated interferon alfa-2b versus -2a on page 105 but the reviewer is probably referring to comparisons of pegylated interferon alfa-2b versus -2a which are evaluated in a different section.</p>
Peer Reviewer 6	4. Results	<p>Definitely has a lot of detail in the article. They include the articles that were reviewed, their description and results. A very extensive search was done and the results reached in this article were the only results that you could have reached based on the evidence.</p>	<p>Thank you. We appreciate your feedback.</p>
Peer Reviewer 1	5. Discussion/Conclusion	<p>Appropriate emphasis is placed on the fact that these recommendations apply only to treatment-naive individuals and does not apply to "difficult-to-treat" populations.</p>	<p>Thank you.</p>
Peer Reviewer 2	5. Discussion/Conclusion	<p>The "future research" section is exceptionally well written and should be easily translated into new research. The implications of the major findings of the study are clearly stated as are the limitations. I do not feel the investigators omitted any important literature.</p>	<p>Thank you. We hope that we were able to adequately set the stage for future research to be done in this area.</p>
Peer Reviewer 4	5. Discussion/Conclusion	<p>I do not have any concerns related to the Discussion section. I think that the implications of the major findings are stated well - in fact, I do not think that my suggestions above will change the results of the implications thereof. The suggestions are intended to make the review more applicable to the population of patients as well as the decision making process that goes on routine practice.</p>	<p>Thank you. Your feedback is appreciated.</p>
Peer Reviewer 5	5. Discussion/Conclusion	<p>yes the future research section is very clear, although there is no mention of genetics as part of future research. With the IL28 story and other SNPs and genome wide surveys, a statement about host issues in treatment response are important</p>	<p>Thank you for your comment. We have addressed this by adding a sentence to the Future Research section stating: "Studies that evaluate the usefulness of genomics and other methods for individualizing treatment decisions in patients with HCV infection are also needed."</p>

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 6	5. Discussion/ Conclusion	This is where the article did an excellent job in discussing the limitations of the available evidence and lists gaps and areas for future research using a different population that may be able to answer the questions more precisely.	Thank you.
Vertex, Public Reviewer	5. Results (p.37)	PROVE-1, sample size of 3,070 patients is not correct, actual n=250., ILLUMINATE, sample size of 322 should be n = 540.	Thank you for pointing out the error regarding the PROVE-1 trial. We mistakenly had the sample size from another trial (IDEAL) by the same author. This error has been corrected. The sample size for ILLUMINATE is corrected—although 540 patients entered into the trial, only 322 achieved an early virological response and were actually randomized to different treatments and analyzed.
Richard Chapell for Merck & Co., Inc, Public Reviewer	5. Results (p.40)	Typographical errors. Please insert a space after colons.	Thank you. Fixed typos.
Vertex, Public Reviewer	5. Results (p.40)	AHRQ reports that two trials found boceprevir was associated with no difference in likelihood of SVR in patients with lower viral load. This was also true of patients with cirrhosis.	This is reported in the results already ("Although triple therapy with boceprevir was not associated with improved likelihood of SVR in the subgroup of patients with advanced fibrosis or cirrhosis, the number of patients randomized to triple therapy was small (n=30) and the estimate was imprecise (pooled RR=1.1, 95% C I 0.55 to 2.1).") Because the sample was so small it is not possible to draw firm conclusions about efficacy in this population, and we did not summarize these results in the Summary bullet points or Summary table.
Richard Chapell for Merck & Co., Inc, Public Reviewer	5. Results (p.43)	Triple therapy with Telaprevir was associated with increased risk of anemia. This increased risk goes unmentioned in several places in the document, noted above, in which increased hematological adverse events with Boceprevir are noted. Please resolve this inconsistency.	Please see responses to other similar comments by this reviewer.

Commentator & Affiliation	Section	Comment	Response
Richard Chapell for Merck & Co., Inc, Public Reviewer	5. Results (p.46)	"In addition, more patients randomized to boceprevir triple therapy used erythropoietin (43% and 87%) compared with those randomized to dual therapy (24% and 33%), which could have attenuated the risk estimate for anemia." This comment is speculative and inaccurate. Anemia rates were calculated based on clinician adverse event reports. It is unlikely that a clinician would consider anemia to be sufficiently severe as to require treatment with erythropoietin but not severe enough to be considered an adverse event. For nearly all treatment groups, rates of anemia were higher than rates of erythropoietin use. We request that the statement be removed.	We do not believe it is clear whether clinicians would have reported anemia in patients who received erythropoietin, if the erythropoietin was used for relatively mild anemia (parameters for erythropoietin use were not reported). However, we agree that it is not clear whether this would have affected risk estimates, so we deleted the last part of the sentence ("...which could have attenuated the risk estimate for anemia.")
Vertex, Public Reviewer	5. Results (p.46)	The report should recognize that in the twelve week regimen of triple therapy with telaprevir compared with dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks, no erythropoietin was allowed in the study.	We appreciate the comment. Because the trial found no difference in risk of anemia between triple therapy with telaprevir and dual therapy, we do not think it is necessary to include additional information about use or non-use of erythropoietin.
Vertex, Public Reviewer	5. Results (p.48)	The sentence "A trial of extended early virologic responders...randomized to 4 compared with 28 more weeks of dual therapy" should read "...randomized to 24 compared with 28 weeks of dual therapy".	The information provided is accurate. In the ILLUMINATE Trial patients with an early virological response were randomized at week 20 to either 4 additional weeks or 28 additional weeks of therapy. We revised the text to be clearer that the randomization occurred at week 20.
Peer Reviewer 1	6. Clarity/Usability	Well written and organized.	Thank you.
Peer Reviewer 2	6. Clarity/Usability	This report is well organized and the main points are very clearly presented. I feel the conclusions can and will be used to inform both policy and practice decisions as well as new clinical guideline development.	Thank you. Our aim was to present the evidence clearly and concisely for future decisionmakers to use.
Peer Reviewer 4	6. Clarity/Usability	Yes, although I do have some suggestions. The authors present the summary of the findings first and then delve into the detailed results. I like this approach, but just to keep the reader oriented, will recommend clearly indicating this using headers (such key question 2; summary of the evidence; detailed results, etc.) Also, will prefer if references are added to the summary statements	Thank you for your suggestions on organization of the text. We are always looking for ways to improve the readability of our reports and will take this into consideration.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 5	6. Clarity/Usability	The report is very detailed and well organized. The volume of material is immense and looking at a paper print out would be important to make sure this readable in a journal format.	Thank you for your comment.
Peer Reviewer 6	6. Clarity/Usability	I think that the conclusions are very helpful and that they can definitely be used to inform reviewers of grant proposals as to where the major gaps are relative to Hep C.	Thank you for your comment.
Dolph Chianchiano, Public Reviewer	6. Discussion	The Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease (CKD) from Kidney Disease Improving Global Outcomes (KDIGO) recommend PEG-IFN and ribavirin combination therapy only for patients with CKD stages 1 and 2, in part because the Food and Drug Administration package inserts for these agents permit their use at this level of kidney function and studies of PEG-IFN and ribavirin excluded subjects with serum creatinine values 1.5 times the upper limit of normal. The Food and Drug Administration suggests that ribavirin be avoided in patients with creatinine clearance less than 50 mL/min because ribavirin is cleared by the kidneys and can cause life-threatening hemolytic anemia. Thus, patients with CKD Stages 3 to 5 may be treated with PEG-IFN or IFN monotherapy. These recommendations are consistent with those published by the AASLD and the AGA. The AASLD guidelines also recommend against antiviral treatment after kidney transplantation.	Thank you for your comment and suggestions for references. The Applicability section of the Discussion notes that the results of the review are not applicable to hemodialysis patients and post-transplant patients since they were excluded from the review. We added a sentence to this section noting that antiviral therapy is not recommended after kidney transplantation and that ribavirin is not recommended in patients with more severe (stage 3 to 5) kidney disease.

Commentator & Affiliation	Section	Comment	Response
<p>Martha Saly, Public Reviewer</p>	<p>6. Discussion</p>	<p>The protease inhibitors that the FDA approved in 2011 can arrest this virus. Protease inhibitors, when added to standard dual therapy, are associated with substantially higher sustained virologic response rates (SVR) and potentially shorter duration of therapy. The draft review cites new evidence demonstrating an association between achievement of SVR and reduced risk of all-cause mortality, supporting the validity of SVR as a surrogate endpoint in HCV. These recent developments in antiviral therapies will have a strong impact on the real-world effectiveness of treatment for those who have been diagnosed with chronic HCV infection. Given the evidence, coupled with the robust research landscape aimed at developing even more effective interferon-free HCV treatment regimens in the near future, the National Viral Hepatitis Roundtable calls on AHRQ and USPSTF to support a public health agenda to eliminate the hepatitis C epidemic. USPSTF recommendations guide clinical practice and reimbursement; without supportive guidelines from the USPSTF, hundreds of thousands of patients will be at significant risk for disease progression and death.</p> <p>The draft review notes that the USPSTF will consider this treatment review together with its screening review in its update, providing a basis and rationale for USPSTF to change its current HCV screening recommendations. As patient advocates, we see a clear and logical association between testing, treatment, and clinical outcomes: patients can't be treated unless they have been diagnosed, and patients who are diagnosed late or not at all face substantial morbidity and mortality – risks which can be significantly reduced by successful treatment.</p>	<p>Thank you for your feedback. It is helpful to know what is the most useful for readers to see in a report of a CER or evidence review. This report will be used by the USPSTF in an independent process to inform its updated recommendations on HCV screening.</p>

Commentator & Affiliation	Section	Comment	Response
Stephen Arcona (Novartis Pharmaceuticals Corporation), Public Reviewer	6. Discussion	Please consider adding the following statements to the second paragraph in the Future Research section of the draft report: "Clinical trials and comparative effectiveness research that examine the efficacy of these new drugs and new regimens in patients with hepatitis C viral infections who were nonresponsive to their initial antiviral treatment may help provide clinicians with a clearer understanding of the differences between current therapies and new drugs/regimens that are in development."	Thank you for this comment. While treatment of antiviral-experienced patients is an important clinical issue, that population was excluded from this report, and we do not think it is appropriate to make future research suggestions for patients that were not addressed in the review.
Vertex, Public Reviewer	6. Discussion (p.60)	The last sentence at the bottom of the page, ending with "...triple therapy approaching the 70% to 80% observed for dual therapy for patients with genotype 2 or 3 infection" should read "...triple therapy approaching 63% and 75%, similar to what has been observed in patients with genotype 2 or 3 infection treated with dual therapy".	This sentence states: "Recent trials found triple therapy regimens with boceprevir or telaprevir, pegylated interferon (alfa-2a or -2b), and ribavirin each associated with substantially higher SVR rates than standard dual therapy with pegylated interferon (alfa-2a or -2b) plus ribavirin in treatment-naïve patients with genotype 1 infection, with SVR rates with triple therapy approaching the 70% to 80% percent rates observed for dual therapy in patients with genotype 2 or 3 infection." These results are accurate and supported by the references provided. The 63–75% range the reviewer is referring to appears to refer to SVR rates with triple therapy regimens; what is reported here are the SVR rates with dual therapy in patients with genotypes 2 and 3 infection.

Commentator & Affiliation	Section	Comment	Response
Richard Chapell for Merck & Co., Inc, Public Reviewer	6. Discussion (p.61)	Page 61: "On the other hand, triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir..." Please note that Telaprevir is also associated with increased risk of anemia. Here, and at other places throughout the document, it is strongly implied that only boceprevir is associated with increased risk of anemia. This creates a false impression in the mind of the reader. This false impression is further reinforced by the consistent pairing of hematological adverse events associated with Boceprevir with rash associated with Telaprevir. The implied equivalence is false as Boceprevir is not associated with rash (See Table 9) while Telaprevir is associated with increased risk of anemia (Table 10). Please revise this sentence and other similar sentences throughout the document (noted above) to eliminate this false impression. Page 69: "... specific harms associated with use of these drugs (such as hematologic adverse events with boceprevir..." As noted on pages 46 and 47 of this review, hematologic adverse events are not specific to Boceprevir. Please revise this statement to eliminate this false impression.	Thank you. We have clarified these points.
Genentech, Public Reviewer	7. References	Recheck and correct citations and bibliography. On Page 17, the last citation number 51 is incorrect. The last statement on this page refers to reference number 52 within the bibliography. We recommend that AHRQ correct this and review other citations in the report to ensure its overall accuracy.	Thank you for bringing this to our attention. We will revise our references to ensure correct numbering.
Richard Chapell for Merck & Co., Inc, Public Reviewer	7. References	Please note that the references are incorrectly numbered.	Thank you for bringing this to our attention. We will revise our references to ensure correct numbering.
Richard Chapell for Merck & Co., Inc, Public Reviewer	8. Figures	Figure B: It is unusual for a study flow diagram to break out the number of studies that address each of the Key Questions. We find this innovation helpful and congratulate you for utilizing it.	Thank you for your feedback. It is helpful to know what is most useful for readers to see in a CER report.

References Obtained From Peer Review and Public Comments and Disposition:

- Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical Gastroenterology & Hepatology*. 2011;9:509-16. PMID: 21397729. Disposition: Already included
- Chak E, Talal AH, Sherman KE, et al. Hepatitis C virus infection in USA: an estimate of true prevalence. *Liver Int*; 2011. 31(8):1090-101. PMID: 21745274. Disposition: Background only
- El-Serag HB, Mason AC. Rising Incidence of Hepatocellular Carcinoma in the United States. *New England Journal of Medicine*; 1999. p. 745-50. PMID:10072408. Disposition: Background only
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- El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med*; 2003. p. 817-23. PMID:14623619. Disposition: Background only
- Flamm et al. High sustained virology response (SVR) among genotype 1 previous nonresponders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus peginterferon alfa-2a/ribavirin. Presented at the European Association for the Study of the Liver Annual Meeting in Berlin, Germany; March 30-April 3, 2011. EASL Poster. Available at <http://clinicaltrials.gov/ct2/show/NCT00845065>. Accessed 3/9/12. Disposition: Excluded, wrong population (nonresponders)
- Gordon CE, Balk EM, Becker BN et al. KDOQI US Commentary on the KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in CKD. *American Journal of Kidney Diseases*. 2011. 52(5):811-825. PMID: 18971009. Disposition: Excluded, no original data, excluded population.
- Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *New England Journal of Medicine*. 2009 Apr 30;360(18):1839-50. PMID: 19403903. Disposition: already included.
- Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. *New England Journal of Medicine*. 2011;364(25):2405-16. PMID: 21696307. Disposition: Already included.
- McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.[Erratum appears in *N Engl J Med*. 2009 Oct 8;361(15):1516]. *New England Journal of Medicine*. 2009 Apr 30;360(18):1827-38. PMID: 19403902. Disposition: Already included
- Pegasys Prescribing Information (03/09/12). <http://www.gene.com/gene/products/information/pegasys/pdf/pi.pdf>. Disposition: Excluded, no original data (FDA information already included).
- Sroczyński G, Esteban E, Conrads-Frank A, et al. Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. *Eur J Public Health*; 2009. p. 245-53. PMID:19196737. Excluded: Wrong study design (cost-effectiveness)