Author's response to reviews

Title: The ongoing impacts of hepatitis C infection: a systematic review of the literature

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Author's response to reviews: see over
5 July 2012

The Editors
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BioMed Central
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Dear Editors

Thank you for allowing me to respond to the Reviewers’ comments. I have addressed every point in order below and have described all the resultant changes to the manuscript under each point. I can confirm that the Additional Editorial Requirements have also been complied with.

Regards

Dr Emma Miller

Referee 1: Response

Title: Living with hepatitis C infection: a systematic review of the literature
Version: 2 Date: 15 May 2012
Reviewer: Michael Wilson

Major compulsory revisions:

1. The authors should consider better clarifying their methods so that the search can be duplicated by readers. Although the search terms are specified precisely, the exact inclusion and exclusion criteria are more unclear. For instance, given that the focus of the review is on living with Hepatitis C, why would the authors exclude clinical evaluation (but then include “clinical impact” in their results)? What does clinical evaluation mean anyway? How does clinical evaluation differ from investigating the personal/social impact of disease? And if the authors really do not wish to include clinical evaluation, why include results about the progression of the disease, psychological well-being, transmission, viral clearance, and mortality?

- We agree that our description of the exclusion criteria could have been less vague. In particular, the use terms such as ‘clinical evaluation’ and ‘clinical impact’ may have confused the issue. Our exclusions applied to RCTs that focused on comparing the performance of different drug therapies or diagnostic technologies with a gold standard, but did not attempt to measure the impact on the trial participants. For instance a study by Thomson et al (2009) compared the sensitivity of reverse transcriptase PCR (RT-PCR) versus antibody screening for the diagnosis of early HCV infection in HIV-positive patients and estimated the length of time from HCV infection to the
development of anti-HCV antibodies. The study was not included because it the focus of the investigation was solely a retrospective serological analysis with no report on the impact on the patients involved. Similarly, a study by Torti et al (2005) comparing regimens of HAART in HIV-HCV coinfected patients was excluded because this study was almost entirely focused on biochemical outcome as the primary endpoint, with no data provided on the clinical/health outcome for patients. Conversely studies that provided data on the effect of antiviral treatment in general on health status during and after treatment were included. Examples include Evon et al (2009) and Bonkovsky (2007) who specifically investigated treatment impact on quality of life. Also included were a number of studies that compared participant health outcomes over time (e.g. fibrosis, liver specific and all cause mortality, post transplant HCV recurrence, etc).

1.a At the reviewer’s suggestion we have now clarified our methods as follows (change is in italics), end first paragraph of ‘Methods’ section:

“We limited the search to primary studies in adults and excluded clinical evaluation or intervention studies that focused on the performance of experimental interventions or diagnostic tools.”

Changed to:

“We limited the search to primary studies in adults and excluded investigations that focused solely on evaluating the performance of diagnostic tools and experimental interventions without providing retrievable data on patient health outcome beyond biochemical or serological endpoints.”

1.b ‘Methods’ section, second paragraph, third sentence changed from:

“Studies were excluded if specific data on hepatitis C outcomes were not retrievable”

Changed to:

“Studies were excluded if specific data on hepatitis C outcomes were not retrievable (for example, in a study of liver disease in general).”

1.c We have also included an additional box which sets out the specific inclusion and exclusion criteria for greater clarity.

**Box 2: Specific Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary studies</td>
</tr>
<tr>
<td>• Adult participants</td>
</tr>
<tr>
<td>• Specific hepatitis C specific data provided</td>
</tr>
<tr>
<td>• Publication between January 1, 2000 and December 31, 2009</td>
</tr>
</tbody>
</table>
- English language

Exclusion criteria
- Data not provided on participant health outcome (beyond serologic endpoints)
- Relevant outcome data not retrievable
- Non-English language
- Previously published analyses of the same data

- What does it mean to exclude experimental studies (page 6)? Does this mean that the authors included only expert consensus or reviews?

1.d Please see our comment regarding our previous use of unclear nomenclature, we have revised the relevant statement, ‘Methods’ section, last paragraph, on page 6, changes from:

“As this review aimed to determine if it was possible to build a picture of at summarising the evidence from observational studies (using both quantitative and qualitative approaches) and experimental or intervention studies were specifically excluded, the quality assessment was restricted to the completeness of information provided by the authors. For instance, studies...”

Changed to:

“As this review aimed to determine if it was possible to build a picture of the trajectory of a hepatitis C diagnosis by summarising the evidence from a broad range of eligible studies (using both quantitative and qualitative approaches), the quality assessment was restricted to the completeness of information provided by the authors. Studies...”

- Why exclude intervention studies (page 5) “that focused on the performance of experimental interventions” (presumably drug-related)? Isn’t the fact that an SSRI can relieve many of these symptoms relevant for the topic of “Living with Hepatitis C”? Does this conflict with the later section (page 10) on “Health outcomes after antiviral treatment or liver transplant”?

1.e Please see the change described 1.a above in which we have clarified our statement concerning experimental interventions (i.e. sentence end of Methods section first paragraph, page 5, now states:

“We limited the search to primary studies in adults and excluded investigations that focused solely on evaluating the performance of diagnostic tools and experimental interventions without providing retrievable data on patient health outcome beyond biochemical or serological endpoints.”

- How were the inclusion/exclusion criteria applied? Was this by consensus of the authors? If so, was a kappa score calculated, and how were disagreements handled?
How were categories assigned to relevant publications? Was this by consensus of the authors? If so, was a kappa score calculated, and how were disagreements handled?

- Since observational, non-randomised and many qualitative studies were used in this review with the aim of including and summarising as much information as possible, kappa scores were not derived. It is important to note that kappa statistics are not currently recommended as standard for Cochrane reviews involving RCT studies. Instead, the inclusion and exclusion criteria were developed by consensus of the authors and applied strictly as developed by team members with ongoing reporting to, and the oversight of, the research team. Where disagreements arose about included or excluded studies, the team reached a consensus through discussion.

- The research team used a process of ‘emersion’ in developing the categories assigned to relevant publications. The two distinct search strategies provided the framework for the categories, which were again developed in consensus with the team. As is discussed in the Cochrane Handbook ([http://www.cochrane-handbook.org/](http://www.cochrane-handbook.org/)) the synthesis of qualitative and other non-randomised data is an aggregative and interpretive process that requires transparency, but nonetheless does remain an area of debate and evolution. We agree that it important to achieve transparency of methodology, and have included the following:

1. End last paragraph of ‘Methods’ section, page 6, changed from:

   “Eligible studies were then summarised and reviewed by the research the team before narrative synthesis. See Additional file 1 for the full list of included articles, as well as their tabulated summaries.”

   Changed to:

   “Inclusion and exclusion criteria were developed by consensus of the authors as were the categories assigned to the reviewed studies. Eligible studies were then summarised and reviewed by the research team, before coding into the specified categories for narrative synthesis. See Additional file 1 for the full list of included articles, as well as their tabulated summaries.”

2. Perhaps because of my difficulty in understanding exactly which articles were included in the study, I have identified a number of articles that seem as if they should have been included but do not appear in the authors’ reference lists:


- This study was found with both of our search terms and is now included. It was excluded from our first search because it was not a follow up design, and from our second because it focused on quantifying symptoms only. On revision 26 such studies are now included.

This study was found with our search terms and is now included. It was excluded because it focused on quantifying symptoms only. On revision 26 such studies are now included.


These two studies were found with our search terms but were excluded because focuses on liver disease with no data on hepatitis C provided


This study was found with our search terms and is now included. It was previously excluded because it focused on quantifying symptoms only. On revision 26 such studies are now included.


This study predates the specific inclusion time frame (i.e. from Jan 1st, 2000)

Additional notes:

- Because this review included well over 200 studies, our submission includes the document ‘Additional file 1.’ We had hoped that this file would prove to be a valuable resource for anybody interested in this area, since all 264 of the included studies are there summarised and tabulated into categories. A full bibliography of the included studies also appears at the end of that document.
- I would greatly appreciate advice from the editors about how to make the existence of this Additional file clearer to the reader.

We agree with the reviewer that symptoms should be regarded as an important impact on the lives of people with hepatitis C and have now included 26 studies that were previously summarised but subsequently excluded on the basis of this sentence.

Changes made:

Table 6 (‘Health related quality of life in untreated chronic hepatitis C infection’) now includes the following entries:
The associated changes in the text are as follows (changes in italics):

1st sentence under subheading ‘Quality of life in untreated hepatitis C’, in ‘Results’ section, page 12:

“Sixty six studies investigated quality of life (QoL), including eight cohort studies in people undergoing treatment also identified in the biomedical literature. Forty five of these studies measured QoL impacts in untreated chronic infection in community-based and clinic populations...”

Added after last sentence of second paragraph under subheading ‘Quality of life in untreated hepatitis C’, in ‘Results’ section, page 12:

“Two studies led by Kramer[37,38] both found reduced QoL in hepatitis C which was associated with fatigue, but not with observed slight neuro-cognitive impairment. Fatigue and depression accounted for the majority of variance in QoL scores noted. Fatigue associated with impaired physical QoL and social relationships, depression associated with lower environmental QoL (eg satisfaction with home, transport, health care access and quality, etc).

Changes made:

Additional file: Table 7(‘Health related quality of life during and after treatment/transplant for hepatitis C infection’) now includes the following entry:

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Country</th>
<th>Population (n)</th>
<th>Main QoL. measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer et al (2002)(^{36})</td>
<td>Austria</td>
<td>Clinic patients (100)</td>
<td>HR-QoL (SF-36):fatigue (FIS) &amp; neuro-cognitive Function</td>
<td>Significantly reduced QoL relative to population norms. Slight but significant neuro-cognitive impairment in HCV not associated with disease activity, fatigue or QoL.</td>
</tr>
<tr>
<td>Kramer et al (2005)(^{37,38})</td>
<td>Austria</td>
<td>Clinic patients (120)</td>
<td>HR-QoL (SF-36):fatigue (FIS) &amp; neuro-cognitive function</td>
<td>Significant fatigue in HCV independently associated with reduced QoL, but not with brain dysfunction.</td>
</tr>
<tr>
<td>Marcellin et al (2007)(^{39})</td>
<td>France</td>
<td>115 HIV-HCV coinfected patients</td>
<td>HR-QoL (WHOQOL-HIV Bref ), depression</td>
<td>Fatigue and depression accounted for the majority of variance in QoL scores noted. Fatigue associated with impaired physical QoL and social relationships, depression associated with lower environmental QoL (eg satisfaction with home, transport, health care access and quality, etc).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Country</th>
<th>Population (n)</th>
<th>Main QoL. measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilsabeck et al (2005)(^{190})</td>
<td>US</td>
<td>Pre (30) &amp; post treatment (11)</td>
<td>HR-QoL (SF-36) Depression/anxiety (BDI-II, BAI), cognitive function (SDMT &amp; TMT)</td>
<td>Treatment associated with reduced cognitive abilities.. QoL at baseline did not differ between Tx groups. QoL impact of Tx not reported.</td>
</tr>
</tbody>
</table>
The associated changes in the text are as follows (changes in italics):

1st sentence under subheading ‘Quality of life related to hepatitis C treatment’, in ‘Results’ section, page 14:

“Twenty two studies investigated health related QoL in patients undergoing antiviral treatment or liver transplantation...”

Added to middle of 1st paragraph under subheading ‘Quality of life related to hepatitis C treatment’, in ‘Results’ section, page 14:

“One study found no difference in QoL between treated and untreated groups but did find that concurrent treatment had a negative impact on cognitive abilities.[43]”

Additional file: Table 8 (‘Psychosocial experience of living with hepatitis C infection’, Subheading ‘Health and Wellbeing’) now includes the following entries:

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Country</th>
<th>Population (n)</th>
<th>Main QoL measures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dwight et al (2000)214</td>
<td>US</td>
<td>50 HCV patients</td>
<td>Quantitative study involving structured psychiatric interviews and validated questionnaires including MAF-FQ &amp; SF36</td>
<td>28% had depressive disorders not correlated with disease severity or demographics. Severity of depression correlated with fatigue level. Concludes disability and fatigue more related to depression than hepatic disease.</td>
</tr>
<tr>
<td>Forton et al (2002)215</td>
<td>UK</td>
<td>27 HCV-RNA+ &amp; 16 HCV-cleared patients</td>
<td>Quantitative study, involving cognitive assessment; QoL, fatigue &amp; depression questionnaires</td>
<td>RNA+ impaired on more cognitive tasks. Impairment not accounted for by depression, fatigue, or IDU history. Suggests biological cause</td>
</tr>
<tr>
<td>Glacken et al (2003)217</td>
<td>Ireland</td>
<td>28 HCV+ people</td>
<td>Qualitative study involving in-depth interviews particularly focusing on fatigue</td>
<td>Fatigue is multidimensional with 2 distinct types – chronic and idiopathic. Universally experienced as ‘whole-body sensation’. Suggests an HCV cause of fatigue that is perpetuated by secondary factors such as inactivity, pain and disability</td>
</tr>
<tr>
<td>Golden et al (2005)218</td>
<td>Ireland</td>
<td>90 HCV clinic patients</td>
<td>Quantitative study, involving structured psychiatric interviews and validated questionnaires including SCID-CV</td>
<td>High prevalence of undiagnosed mood disorders. Depression associated with adverse experiences of illness</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Subjects</td>
<td>Methodology</td>
<td>Findings</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Goulding et al (2001)(^{219})</td>
<td>Ireland</td>
<td>77 HCV clinic patients</td>
<td>Quantitative study, involving structured clinical examination &amp; history FIQ and HADS</td>
<td>Moderate increase in fibromyalgia in HCV with number of tender points associated with mode of acquisition. Anxiety &amp; depression higher in HCV, possibly related to psychological factors.</td>
</tr>
<tr>
<td>Hassoun et al (2002)(^{222})</td>
<td>Canada</td>
<td>92 HCV patients</td>
<td>Quantitative study, involving Demographic &amp; clinical data, Assessing fatigue with the FIS</td>
<td>67% had fatigue – described as ‘frequent and disabling’. Significantly increased compared to controls, fatigue not associated with disease activity or progress.</td>
</tr>
<tr>
<td>Hilsabeck et al (2002)(^{223})</td>
<td>US</td>
<td>66 HCV &amp; 14 HCV-patients with liver disease</td>
<td>Quantitative study, involving assessment of four cognitive functions using validated cognitive tests</td>
<td>Significant cognitive difficulties for both patient groups associated with liver fibrosis but still higher in HCV with and without cirrhosis.</td>
</tr>
<tr>
<td>Hilsabeck et al (2003)(^{224})</td>
<td>US</td>
<td>21 HCV patients</td>
<td>Quantitative study, involving assessment of four cognitive functions using validated cognitive tests</td>
<td>Significant cognitive difficulties not related to psychiatric symptoms. Cognitive impairment level sufficient to impact on QoL.</td>
</tr>
<tr>
<td>Kozanoglu et al (2003)(^{228})</td>
<td>Turkey</td>
<td>95 HCV patients &amp; 95 HCV- patients</td>
<td>Quantitative study of demographic, clinical data, information on fibromyalgia</td>
<td>Higher prevalence of fibromyalgia syndrome (FS) in HCV with more tender spots with higher pain intensity compared to controls with FS.</td>
</tr>
<tr>
<td>Lang et al (2006)(^{230})</td>
<td>Australia</td>
<td>Phase 1 - 73 people with HCV; Phase 2 - 188 people with HCV</td>
<td>Phase 1 – focus groups &amp; individual interviews. Phase 2 – quantitative surveys and serology</td>
<td>Tiredness, irritability, depression, mental tiredness &amp; abdominal pain most prevalent symptoms. 4 symptom ‘clusters’: neuropsychiatric; gastrointestinal; algesic (e.g. joint &amp; muscle pain); and dysthetic (e.g. noise/light sensitivity, skin problems)</td>
</tr>
<tr>
<td>Lehman et al (2002)(^{231})</td>
<td>US</td>
<td>120 veterans with HCV</td>
<td>Quantitative study, involving surveys, demographic &amp; clinical data</td>
<td>Depression in 44%, anxiety in 38%, post traumatic stress disorder 21%; alcohol-related problems 27%. All outcomes positively correlated with each other.</td>
</tr>
<tr>
<td>McAndrews et al (2005)(^{232})</td>
<td>Canada</td>
<td>37 HCV patients &amp; 46 HCV- controls</td>
<td>Quantitative study involving radiographic, clinical and neuropsychologic assessment</td>
<td>Marginally reduced learning efficiency in HCV not associated with increased fatigue and depression in this group. HCV group had changes in brain metabolites, not associated with liver histology and not explanatory of ‘brain fog’ reported by</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Country</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Findings</td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>McDonald et al (2002)</td>
<td>Australia</td>
<td>115 HCV clinic patients</td>
<td>Quantitative study, involving surveys, demographic &amp; clinical data</td>
<td>Fatigue in 83%, all the time in 31%, psychopathology in 50%. Fatigue weakly correlated with liver histology but strongly correlated with all psychological domains, particularly depression.</td>
</tr>
<tr>
<td>McKenna et al (2009)</td>
<td>Ireland</td>
<td>290 people with iatrogenically acquired HCV</td>
<td>Quantitative survey of socio-demographic and clinical characteristics</td>
<td>After mean 26 years infection 62% hepatic &amp; 99% extra-hepatic symptoms. Fatigue in 88% and pain in 96%. 89% reported diagnosed co-morbid diseases. Reported symptoms associated with age, female sex, and co-morbidities.</td>
</tr>
<tr>
<td>Nagano et al (2004)</td>
<td>Japan</td>
<td>69 HCV patients</td>
<td>Quantitative study involving clinical and demographic data, ‘stress inventory’</td>
<td>All stress inventory scales related to the ‘type 1’ personality (low sense of control, objective dependence of loss, unfulfilled need for acceptance, altruism) associated with severity of disease (according to ALT and liver cirrhosis). Chronic stress related to type 1 personalities might influence HCV progression.</td>
</tr>
<tr>
<td>Obhrai, et al (2001)</td>
<td>US</td>
<td>149 HCV+/– patients with/without alcohol problems and/or liver disease</td>
<td>Quantitative study, involving surveys, demographic &amp; clinical data</td>
<td>Fatigue higher in HCV cf other groups (not statistical) but did not improve with rest as effectively. Fatigue and psychological symptoms more common, severe and less responsive to remedies in HCV.</td>
</tr>
<tr>
<td>Piche et al (2002)</td>
<td>France</td>
<td>78 HCV patients, 22 HCV- controls, 13 biliary cirrhosis patients</td>
<td>Quantitative study, involving surveys (FIS), demographic &amp; clinical data</td>
<td>Fatigue higher in HCV and more in females. Correlated with leptin (as in biliary cirrhosis) but not age, liver function, or viral load.</td>
</tr>
<tr>
<td>Poynard et al (2002)</td>
<td>France</td>
<td>1614 HCV patients</td>
<td>Quantitative study, retrospective analysis of demographic, clinical, virologic, immunologic and other data</td>
<td>Fatigue in 53%, severe enough to impair activity in 17%, independently associated with female sex, age &gt; 50 years, cirrhosis, depression and purpura.</td>
</tr>
<tr>
<td>Silberbogen et al (2007)</td>
<td>US</td>
<td>29 veterans with HCV (32% on Tx)</td>
<td>Quantitative study, involving data on pain (MPQ- SF; WHYMPI; NRS) &amp; depression (CES-D)</td>
<td>Pain reported in 83%, most in upper limb, hip, lower limb &amp; lower back. Alcohol and smoking associated with pain and depression in HCV.</td>
</tr>
<tr>
<td>Weissenborn et al</td>
<td>Germany</td>
<td>30 HCV patients with</td>
<td>Quantitative study, involving</td>
<td>Some cognitive impairment.</td>
</tr>
</tbody>
</table>
fatigue, 15 HCV-controls

neurological & neuropsychological assessment, EEG, MRI & MRS

higher anxiety and depression (none had cirrhosis or fibrosis) Evidence of central nervous system involvement (per MRI), associated with higher severity of fatigue


306 veterans with HCV

Quantitative study, retrospective analysis of past & present DSM-IV based psychiatric disorders recorded in clinical database

Mood disorders in 38%, personality disorders in 30%, post traumatic stress disorder in 19% and other in 17%. 86% diagnosed with alcohol disorders & 28% with IDU history (noted high prevalence of psychiatric disorders exist in veterans)

The associated changes in the text are as follows (changes in italics):

1st sentence under subheading ‘Psychosocial experience of living with hepatitis C infection’ (previously ‘Social experience of living with hepatitis C infection’), in ‘Results’ section, page 14:

“We identified 43 studies investigating the personal experience of living with ongoing hepatitis C infection, including its impact on social functioning, lifestyle, and health and well-being...”

End last paragraph under subheading ‘Psychosocial experience of living with hepatitis C infection’ (previously ‘Social experience of living with hepatitis C infection’), in ‘Results’ section, section started page 14:

“A number of studies investigated specific symptoms of hepatitis C infection – with fatigue being the most common, followed by depression and other mental health issues. Bodily pain, particularly in the form of myalgia and a degree of cognitive impairment was also identified by several authors. The majority of studies found symptoms were independent of disease activity or disease severity, but associated with depression, anxiety and other psychosocial factors. The direction of causation might prove difficult to untangle, particularly where specific symptoms are tightly clustered. Golden et al, [58] for instance, found that mood disorders were highly prevalent in hepatitis C, and depression was associated with experiences of illness – including stigma, poor adjustment to the diagnosis and physical symptoms. There were three studies, however, that suggested a biological cause for a slight cognitive impairment observed in hepatitis C. [59-61]”

- Please note that all references in the text and figures have also now been updated to reflect the 26 described additions.

3. If the focus on the paper is “Living with Hepatitis C,” why would the authors include populations who do not have HCV (but are merely “at risk”)?
We used this phrase because we also including transmission studies in our search to examine the risk for disease, however, we focussed entirely on outcomes for people with hepatitis C. We agree that this could be more clearly stated.

3.a From last line of page 4, ‘Introduction’ section, changed from:

“Specifically, we searched for studies in adult persons with or at risk for hepatitis C infection in which health or social outcomes of infection were investigated (including studies of hepatitis C transmission).”

Changed to:

“We searched for studies on hepatitis C in adult persons in which the health or social outcomes of infection were investigated (including studies of hepatitis C transmission).

• Please note: the Abstract was also updated to reflect this change.

4. Although the authors’ point is appreciated on page 8, namely that primary physicians can improve care for patients with this disease, how does monitoring ALT fit into the authors’ primary focus on living with HCV?

We accept that the point isn’t immediately aligned with the primary objectives of the review, yet it was essentially raised as an interesting observation reflecting the dichotomy between the established literature and the reality of practice. While not directly impacting on the patient’s experience of living HCV, unless monitoring of ALT was an expectation, absence of monitoring in the long run might ultimately impact on health outcome. We have included an additional sentence clarifying the issue.

4.a Inserted between 2nd to last and last sentence of page 8, ‘Results’ section:

“While unlikely to have direct impact on the experience of living with hepatitis C, a lack of ongoing ALT monitoring might eventually have implications for health outcome in their patients.”

More minor points/discretionary revisions:

5. What does it mean that “All identified abstracts were scanned” (page 6)? Did the authors really read these abstracts quickly? How many authors were involved in reading through abstracts?

By ‘scanned’ is indeed meant that all identified abstracts were read quickly to establish their relevance to the review bases on the search strategy that was developed in consultation with the research team. This lead author undertook the scanning process, retrieved the full text articles and reported on the outcome to the research team, who were able to assess the sensitivity of the process according to their respective areas of expertise and knowledge of the literature.
6. What does it mean that “there was no duplication between the two sets of search terms” when there were 8 duplicate studies identified? (page 6)

The sentence currently raises the exception of the eight but we have now further clarified this as below.

6.a 2nd sentence of ‘Results’ section, page 6, changed from:

“With the exception of eight studies (all of which investigated health related quality of life), there was no duplication between the two sets of search terms.”

Changed to:

“With the exception of eight studies (all of which investigated health related quality of life), there was little duplication between the results obtained using the two sets of search terms.”

7. Box 1 should be included with the results, and likely integrated with Figures 1 & 2 (page 5).

This information was provided according to the PRISMA 2009 checklist item for the Methods section – i.e. “Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.” Nonetheless, if the Editor agrees, we would be happy to move this to the results section if the Editor

8. As an extremely minor point, “We selected studies that did not simply describe clinical symptoms…but which focused more closely on the self-reported experience of undergoing treatment for Hepatitis C” (page 10) is self-contradictory. Since “symptoms” are the things reported by patients, there are no symptoms which are not a self-reported experience.

As with our changes at point 2 of Reviewer A, we have accepted that symptoms as measured in, or reported by patients, should be included (26 previously excluded studies have not been reinstated in the review on this basis. Checking our records, however, there were no studies that were excluded on the basis of exploring symptoms alone and so it is difficult to justify this qualifier. The sentence has now been removed.

8.a 2nd sentence under subheading ‘Health related quality of life during the course of antiviral treatment’ in ‘Results’ section, page 10, removed.

9. Headings on page 11 “The social experience of Hepatitis C” and on page 14 are duplicated.

We thank the reviewer for this observation. The page 14 subheading and the table 8 title in the Additional file (page 12) that relates to this section have both been updated to:

“The psychosocial experience of living with hepatitis C infection”
10. The discussion again mentions that literature on “medical and social” aspects of the disease was reviewed. Psychological well-being is not mentioned, despite being included in the search terms.

While appreciating the Reviewer’s comment, we believe that the discussions of findings does include description of the major parameters of the search. Nonetheless, we do accept that the summary descriptions ‘medical’ and ‘social’ literature should be more accurate.

10.a 1st sentence of ‘Discussion’ section, page 17, changed from:

“In this paper we reviewed the medical and social literature on the ongoing impact of diagnoses with hepatitis C infection.”

Changed to:

“In this paper we reviewed the biomedical and social literature on the ongoing clinical and psychosocial impacts of diagnoses with hepatitis C infection.”

11. The authors' points about need for more research is appreciated in the conclusions (page 18). However, I would like a better summary of the articles. What are the important take-home points for the average person (or the average clinician)?

As our additional notes describe under Reviewer 1 question 2 (and reproduced below). All of the included studies are summarised according to the categories forming the subheadings in the text. May we draw the Reviewer’s attention to the Additional file.

**Additional notes**:

- Because this review included well over 200 studies, our submission includes the document ‘Additional file 1.’ We had hoped that this file would prove to be a valuable resource for anybody interested in this area, since all 264 of the included studies are there summarised and tabulated into categories. A full bibliography of the included studies also appears at the end of that document.
- I would greatly appreciate advice from the editors about how to make the existence of this Additional file clearer to the reader.
1. Clarity regarding conceptual framework and objectives
There appears to be a mismatch between the stated objectives and the areas of focus in the manuscript. For example, in the results section of the abstract you open with information on transmission and disease progression risk, which to my reading does not appear to be related to your primary objectives of exploring the social and personal health impacts of living with HCV. So – again, when there are large sections of the manuscript addressing transmission and clinical aetiology/disease progression – this feels incongruent. For example, in the ‘temporal experience of HCV’ section I am unclear how the quant data regarding transmission incidence and prevalence among cohorts of PWID relate to the temporal experience of HCV, or to the social and personal impacts of diagnosis or to the title of the study ‘living with HCV infection’. This mismatch could be rectified by clarifying your objectives and conceptual framework. For example – the objectives section of the abstract reads ‘ongoing personal health and social impacts of diagnoses with HCV’. This is somewhat confusing – are you focusing here on the impacts of diagnosis – which implies a certain aspect of living with HCV and a certain point in time, or on experiences of living with HCV more broadly (implied by your title and the ‘ongoing’)? Even if both – the implication is that the area of focus is on the personal impact of living with HCV (social and physical) or more specifically (on reading the background section) the lived experience of HCV over time from diagnosis, a rich and interesting area of focus. In order to do this subject justice in a review of this type, I would recommend seriously considering the need for sections on transmission of HCV and the natural history of HCV – especially as both draw on clinical/quant data that does not appear to speak to your objectives.

We agree that our lack of clarity in explaining our objectives has resulted in a sense of incongruity between stated objectives and reported. We have amended our title and descriptions of the objectives as per below. I trust that this then strengthens the case for the inclusion of the sections on HCV transmission and natural history since they draw on data more relevant to our stated objectives.

1.a Title change to “The Ongoing Impacts of Hepatitis C: A Systematic Review of the Literature

1.b Last sentence of ‘Background’ section in the abstract, page 4, changed from:

“Making these strategies relevant to the vast majority of those affected by hepatitis C requires a complete understanding of the ongoing impacts of hepatitis C diagnoses.”

Changed to:

“Making these strategies relevant to the vast majority of those affected by hepatitis C requires a more complete understanding of the trajectory of infection with hepatitis C and its ongoing impacts.”

1.c ‘Objectives’ section in the abstract, page 2, changed from:

“We used a systematic approach to scope the literature to determine what is currently known about the ongoing personal health and social impacts of diagnoses with hepatitis C infection and to identify what knowledge gaps remain.”
Changed to last sentence of the ‘Background’ section in the abstract:

“We used a systematic approach to scope the literature to determine what is currently known about the health and social impacts of hepatitis C along the trajectory from exposure to ongoing chronic infection, and to identify what knowledge gaps remain.”

1.d Last line of ‘Background’ section of manuscript, page 5, changed from:

“The objective of this study was to determine what is currently known and identify some of the gaps in our understanding of what it means to live, grow and age with chronic hepatitis C.”

Changed to:

“The objective of this study was to determine what is currently known about the health and social impacts of hepatitis C along the trajectory from exposure to ongoing chronic infection, and to identify what knowledge gaps remain.”

- It is important you define also what you mean by ‘social’ and ‘personal health’. I would expect ‘social’ to include issues such as impact of HCV on intimate and wider relationships, employment opportunities/experiences, benefit access, stigma and discrimination, disclosure, social supports, medical encounters, housing access, criminalisation (for PWID – ie impact of incarceration, treatment access in prison etc), gender issues etc and ‘personal health’ to include areas such as illness management, treatment decision making, treatment access and experiences, symptom experiences etc. While some of these areas are mentioned they appear to be rather cursory – and many are not. Obviously, not all of these issues are adequately covered in the literature – but this could be a point of departure for research recommendations. If these issues are not the focus of your review, then that is completely fine – just clarity around the objectives is needed.

We take the reviewers point and agree greater clarity about the scope and the intent of the review is required. As discussed above, we have amended the title and the description of objectives which may help to address this issue. We have also made changes to the title of the second search strategy and included a clarifying statement about the section.

1.e Title of second search section, in ‘Results’, page 11, changed from:

“The social experience of hepatitis C”

Changed to (now page 12):

“The personal and social impacts of hepatitis C”

1.f First sentence of second search strategy section, in ‘Results’, page 11, changed from:
Our second strategy identified 107 studies investigating the personal experience and social impacts of hepatitis C (see Figure 2).

Changed to:

Our second strategy identified 133 studies investigating the personal experience and social impacts of hepatitis C – in terms of individual wellbeing and psychosocial function (see Figure 2).

1.f. First sentence of section subtitled ‘Psychosocial experience of living with hepatitis C infection’, in ‘Results’, page 14, changed from:

“We identified 21 studies investigating the personal experience of living with ongoing hepatitis C infection, including its impact on social functioning, lifestyle, and health and well-being (see Additional file 1, Table 8).”

Changed to:

“We identified 43 studies investigating the impact of hepatitis C infection on social functioning, lifestyle, health and well-being (see Additional file 1, Table 8).

2. Clarity regarding chosen search strategy, how it relates to objectives and chosen areas of focus.

The methods section is comprehensive, however I was concerned that your search criteria was overly limiting. I imagine that many studies – especially qualitative - that explore/address experiences of living with HCV, may not come up under the terms: quality of life OR social impact OR socioeconomic impact OR psychological wellbeing. Were these terms specific database subject categories, or key words? They appear to come from a psychology disciplinary angle and may preclude articles which focus more on the social aspects of living with HCV. I would be interested in the rationale for these choices and not others such as stigma, disclosure, relationships, gender, treatment experiences etc. I am curious to know what is meant by ‘specific data on HCV outcomes’ and why this was an exclusion criteria. It appears to be a rationale for a review of quantitative literature – however the qualitative literature in this field (which may speak more to your stated objectives) may not include ‘specific data on HCV outcomes’. What exactly is meant by HCV outcomes?

We trust that our earlier described amendments to the objectives and text now resonate better with the chosen areas of focus. The search terms were key words aimed at specifically identifying stated outcomes of HCV rather than fully exploring the lived experience of infection which would be beyond the scope of a single paper. The review was focused on studies that investigated the direct links between social phenomena and HCV, and even so did identify important modifiers of health and wellbeing outcomes including 6 studies on the long term impact of diagnosis; 5 studies specifically focusing on HCV related stigma and discrimination; 5 studies on treatment decisions; and 10 studies on accessing health services (and related discrimination and stigma). These studies are tabulated and summarised in tables 8 and 9 of the Additional file, which also summarises several studies on other identified phenomena such as social support, social isolation, lifestyle choices, social function and gender roles.
In response to Reviewer 1’s similar comment about a similar (see above, on page 1) we have clarified our statement about ‘specific data on hepatitis C outcomes’ as described (see above, on page 2):

1.a ‘Methods’ section, second paragraph, third sentence changed to:
“Studies were excluded if specific data on hepatitis C outcomes were not retrievable (for example, in a study of liver disease in general).”

3. Referencing!
It is imperative that for a review all statements should be adequately referenced. I was surprised to find a number of sections including no references at all. For example the Social experience of living with HCV section was substantially under referenced. Every statement, such as: ‘exaggerated fears of transmission ... reduced intimacy in relationships’ needs references. Can you expand on what you mean by ‘over-emphasised transmission risks’ – for example in which context, over-emphasised by whom? References are also required here. Again, references are required for the lifestyle modifications such as reductions in alcohol. It is unclear whether these lifestyle modifications took place or are just recommended – and then what impact did this have on the individual’s wellbeing? Again these statements need to be referenced. There are no references at all in the paragraph ‘over-emphasised ...was reported’ or that beginning ‘infection with HCV had substantial impacts ...’ – it is important for all these statements to be referenced, and also acknowledgement made of the cases where they do not hold, for example there have been studies that have found that the diagnosis of HCV is part of a biographical flow, and is not experienced as disruptive. A nuanced reading of the literature is required and statements need to be contextualised. For example – the sentence ‘the psychosocial stress ... marginalisation for PWID’ appears to be a supposition bringing together disparate factors from different studies – however, it is hard to tell as not referenced. What is meant by ‘psychosocial stress’ and what other factors may be involved? For example additional factors may include the testing of HCV and HIV at the same time, the positioning of HCV harm reduction within HIV frameworks etc (see papers by Rhodes et al, Harris 2009 etc)

May I draw the Reviewer’s attention to the ‘Additional file’. The text of the manuscript was really to provide a narrative summary of all 264 studies (far too large a reference list for a single manuscript) but which were all summarised and tabulated in the Additional file in categories relating to the subheadings in the manuscript. We do agree, however that more referencing within the document is required and we now have included example references to the specific items identified by Reviewer 2 within the relevant manuscript section (note: section too large to reproduce in this document) and have included them where specific references are made. We trust that this also addresses the contextualisation issues. Please see my repeated ‘additional notes’ below.

Additional notes (copied from above):

- Because this review included well over 200 studies, our submission includes the document ‘Additional file 1.’ We had hoped that this file would prove to be a valuable resource for anybody interested in this area, since all 264 of the included studies are there summarised and tabulated into categories. A full bibliography of the included studies also appears at the end of that document.
• I would greatly appreciate advice from the editors about how to make the existence of this Additional file clearer to the reader.

By ‘over-emphasised transmission risks’, we mean that the risk of transmission unnecessarily inflated in the perception of the person with hepatitis C or their social circle. We have sought to clarify this with an amendment as below:

3.a First sentence of paragraph 2, under ‘psychosocial experience of living with hepatitis C’ subheading, in ‘Results’, page 16, changed from:

“Over-emphasised transmission risks also appeared to result in unnecessary changes in everyday practices, such as refraining from sharing towels and drinking glasses or not taking part in food preparation.”

Changed to:

“Fear of transmission, where the perceived risk is often unnecessarily inflated, also appeared to result in unnecessary changes in everyday practices...”

4. Adequate coverage of the relevant literature and results clarity

It feels as if much of the relevant literature has not been addressed in the latter sections – perhaps due to the somewhat restrictive search criteria and again, an apparent mismatch between the objectives and reported findings is reflected in a somewhat thin coverage of the literature in the ‘the social experience of HCV’ section. What may have been more helpful/interesting for this section or the second search strategy as a whole would have been a meta-analysis of these studies or even demarcation of sections into the primary themes addressed in the HCV social research literature – for example stigma, disclosure, treatment decisions, gendered experiences of living with HCV etc – as these seem to speak so clearly to your overall objectives. While some of these themes are addressed (nothing on gender??) they feel a little thin (much more could be said re treatment decision making for example – and there are more relevant studies during the search timeframe than 5) and could be given sections in their own right. For example, I am not sure the paragraph on stigma, sits well under that of diagnosis as you are referring to stigma in a wider context. The way that structures are productive of stigma such as outlined by Paterson et al., also need to be acknowledged and some demarcation between stigma (felt/perceived) and discrimination made.

Please see the amendments above in response to the comments about the incongruence between the stated objectives and the review content. We trust that this addresses some the concerns restated here. The different sections that the Reviewer proposes do appear already in tabulated form in the ‘Additional File’. The search did identify two papers in the time period on gender and these are referred to in the manuscript and are tabulated in the ‘Additional file.’ Using our specific inclusion and exclusion criteria, I can confirm only five of the identified primary studies on treatment decisions in hepatitis C were identified. Paterson et al (2006) is identified in our search and is included (see Table 9, Additional file, under subheading ‘health service access. In the changes in the text identified below, please see specific reference to that study as follows.
4.a Final subheading, in ‘Results’, page 15, changed from:

“Experiences of diagnosis and management of hepatitis C”

Changed to:

“Responses to diagnosis and management of hepatitis C”

4.b First two paragraphs, under final subheading in ‘Results’, pages 15-16, amended as follows (changes in italics):

“Finally, we identified 26 studies investigating experiences related to diagnosis and treatment (see Additional file 1, Table 9). With some degree of overlap, these studies focused on the immediate impact of diagnosis and perceptions of stigma and discrimination in relation to it, accessing health services and making decisions about treatment. Diagnosis with hepatitis C could be a stressful event, characterised by feelings of shock and devastation that transitioned into enduring emotional, psychosocial and even physical effects. [61] For some, the time of diagnosis was an event equivalent to the stress of events such as moving cities, losing a job, marital breakdown and divorce. [62] Some studies, however, described a more dynamic response that was mediated by changes in social context. [63] For instance, the threat of HIV and issues related to substance use was considered a higher priority in some groups. [64]

The perception of stigma is generally an internalised phenomenon resulting from individually held understandings and interpretations. For instance, study participants described perceptions of stigma resulting from feelings of contamination and fear of disclosure to others, from whom they anticipated rejection, much of which was on the basis of fear of disease transmission. [65] Golden et al [66] found perceived stigma was associated with decreased acceptance of illness, decreased social adjustment and increased reported symptoms in hepatitis C.

Discrimination can flow from the beliefs and attitudes of others and ultimately shape perceptions of stigma through the differential treatment of people with particular conditions. As Paterson et al [66] describe, how illnesses are constructed by health providers influences not only the care offered, but also feeds into the self perception of the affected person. Many study participants reporting negative experiences in health care settings in relation to perceived discrimination. Perceived discrimination was reported in multiple settings, including in interactions with health care services. In one study of over 500 people with hepatitis C, 65% reported having experienced health care discrimination, which was associated with pessimism about future health and decreased social interaction among other things. [67] Perceived discrimination was also found to be a significant barrier to health treatment access, to the extent that refusal of treatment by providers was reported.[68] Harris et al [69] found that reports of refusal or withdrawal of health care were common and contributed to a reluctance to disclose to health professionals even in the context of a perceived obligation to do so.
‘The social experience of HCV’ section contains a sub-section with the same title – this is a little confusing. How are they demarcated?

We both reviewers for this observation. As described above (Reviewer 1, point 9), the page 14 subheading and the table 8 title in the Additional file (page 12) that relates to this section have both been updated to:

“The psychosocial experience of living with hepatitis C infection”

Minor Essential Revisions
2. Background section: Over 170 mill people now chronically infected, the estimate of 160 mill requires updating

2.a Third sentence of first paragraph, in ‘Background’ section, page 4, and its associated reference, changed from:

“Recent estimates put the global hepatitis C prevalence at around 2.4%, with 160 million people now thought to be chronically infected. [3]”

Changed to:

“Recent estimates put the global hepatitis C prevalence at around 2.4%, with up to 170 million people now thought to be chronically infected.[3]”

3. Background section: The second paragraph feels very vague, with many qualifiers. For example, ‘there may be negative social implications within the context of a community who are largely uneducated about HCV transmission’ – what community are you talking about here? Communities of people who inject drugs? The broader public? In which country? HCV is often stigmatised due to its association with injecting drug use – hence there are also negative social implications from correct knowledge about HCV transmission. This paragraph needs to be more concise, and if foregrounding a review contextualised – this is what we already know, this what we are aiming to find out etc... references are needed for ‘disclosure ... workplaces’. This phrase in the following sentence ‘diagnosis and management impacts are influenced ...’ is confusing – not sure what is meant here.

We agree clarification of the social context is important here, and we hope that the following changes improve this paragraph as suggested.

3.a First two sentences of second paragraph, in ‘Background’ section, page 4, changed from:

“The personal impacts of a diagnosis of hepatitis C infection may be significant. The direct effects of the virus on health and wellbeing and its effective management might require people with hepatitis C to make significant lifestyle changes including reducing work hours or alcohol consumption. [9, 10]”

Changed to:
“The personal impacts of a diagnosis of hepatitis C infection are known to be significant. The direct effects of the virus on wellbeing and its management can lead to people making significant lifestyle changes including reducing work hours or alcohol consumption [9, 10] which may in turn influence economic status and social participation.”

3.b Third sentence of second paragraph, in ‘Background’ section, page 4, changed from:

“There may be negative social implications within the context of a community who are largely uneducated about hepatitis C transmission, and prevailing stigmatisation and marginalisation of people who inject drugs – the major risk factor for infection.”

Changed to:

“There can be negative social implications for people living within the context of a broader community who may be largely uneducated about hepatitis C transmission. In most cultures around the world there is prevailing marginalisation of people who inject drugs – the major risk factor for infection.”

3.c We have included the reference for disclosure and workplaces as suggested.

3.d Third from last sentence of second paragraph, in ‘Background’ section, page 4, changed from:

“As with other chronic diseases, diagnosis and management impacts are influenced by a multitude of clinical and psychosocial forces.”

Changed to:

“As with other chronic diseases, experiences of diagnosis and management are shaped by a multitude of physical and psychosocial forces.”

Discretionary Revisions

1. I am curious why you use the term ‘hepatitis C infection’ in the title and body of the manuscript. Possibly consider just using ‘hepatitis C’. Some people living with the virus and community groups find the term ‘infection’ to be offensive/stigmatising – and it is not really necessary.

The full term ‘hepatitis C infection’ may have been overused in this paper – please note that we have replaced it with the simplified term ‘hepatitis C’ where possible throughout the paper.

2. It is unfortunate that there has been lag of a couple of years between when the review was conducted and submission for publication. There has been much written on the subject since, and while I realise this is time consuming the review would be improved if it was updated to include the latest literature. This could potentially be a major compulsory revision dependent on the journals review policy.
Avoiding the time lag would have been preferable but would also desire to avoid further delays. We respectfully await the Editors’ advice on this.

3. Background section: As this is article is aimed at an international journal/audience it is preferable if you open to focus on global figures / impact. If Australia is to be a focus this needs to be stated and justified early on.

We do agree that commencing with a comment about one country is not appropriate. We have now amended the text to commence with a statement regarding the importance of hepatitis C as a global issue and then using the example of Australia:

3.a First sentence, in ‘Background’ section, page 4, changed from:

“Hepatitis C infection is one of the most commonly notified communicable diseases in Australia with an estimated prevalence approaching 1.5%. [1]

“Hepatitis C infection is now acknowledged as an issue of major public health importance for most countries in the world. [1] In Australia, hepatitis C is one of the most commonly notified communicable diseases with an estimated prevalence approaching 1.5%. [2]”

4. The discussion is good and helps to clarify the conceptual framework of the study. A suggestion is to bring some of this forward to the introduction/background section – to provide a rationale for the longitudinal searches.

I trust that the changes made to the objectives and the background in response to the comments of both reviewers has clarified the rationale for both searches.

ADDITIONAL EDITORIAL REQUIREMENTS

(1) Please revise the abstract according to our guidelines (http://www.biomedcentral.com/info/ifora/abstracts). The abstracts of manuscripts submitted to the BMC-series should be structured as follows:

- Background: This should place the study into the context of the current knowledge in its field and list the purpose of the work; in other words, the authors should summarise why they carried out their research.
- Methods: This should summarize how the study was performed and mention the different techniques employed. It should also include details of any statistical tests employed.
- Results: This section should describe the main findings of the study.
- Conclusions: A brief summary of the content of the manuscript and the potential implications of its results.

Please note that potential peer reviewers are only shown the abstract of your manuscript before deciding whether or not to review your work. Abstracts should therefore be long enough, and contain sufficient details to inform the reader of the main aspects of the work. However, abstracts which exceed 350 words may be too complicated to provide a concise overview of the study.

Please make sure to update both the abstract in the manuscript file and in the submission system (Workflow).
(2) We note that the figures have been included in the manuscript file. Please upload the figures as separate figure files using the "upload" form on the submission system only, and delete the figure from the manuscript file. The figure file should not include the title (e.g. Figure 1... etc.) or the figure number. The legend and title should be part of the manuscript file, given after the reference list. Please ensure that the order in which your figures are cited is the same as the order in which they are provided. Every figure must be cited in the text, using Arabic numerals. Please do not use ranges when listing figures. For more information, see the instructions for authors: http://www.biomedcentral.com/info/ifora/figures.

(3) Please add a ?Conclusions? section after ?Discussion?.

(4) All additional files must be mentioned in the text in numerical order, or removed from the system. Please add a section titled "Additional files" at the end of the manuscript (after the tables) listing the following for each file: the title of the data, and a short description of the data.

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 24 June 2012. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/Manuscript/login/man.asp?txt_nav=man&txt_man_id=1370133576665257. You will find more detailed instructions at the base of this email.

All Additional Editorial Requirements have been complied with.