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Title: HCV Cure with DAAs: Clinical, Economic, Societal, and Patient Value for China

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Dear Li-Jun Cui, Science Editor,

Thank you for providing us with the peer reviewers' comments on the above manuscript. We have revised the manuscript according to the recommendations of the reviewers. Please kindly find below a point-by-point response to each reviewer's comments.

We trust that these revisions suitably address the comments of the peer reviewers, and we look forward to hearing the editorial decision.

Yours sincerely,
Shan-Lian Hu

Reviewer 00009848:

Many studies have demonstrated that achieving SVR in CHC patients can improve the long-term outcomes in many aspects in these patients. This MS systemically reviewed the importance of curing HCV from clinical, economic, social, and patient's perspectives in China, a timely topic. It shares some interesting data on HCV in China that are not well known to worldwide hepatology society. It is also important to promote DAA treatment in China and Asian Countries. This reviewer will have the following comments:

Response: We thank the reviewer for providing the detailed comments, as addressed below.

The main comments:

1. The current title is "Curing Hepatitis C: The Clinical, Economic, Societal, and Patient Value for China". As this MS emphasize the value of DAA, the title may need to include "DAA", like Curing hepatitis C with DAAs…."

Response: We have changed the title to "HCV Cure with DAAs…".

2. The authors mentioned there are 10 million CHC patients and many physicians are still using PR for HCV treatment. To better address the value of DAA treatment, it is essential to define the current related issues in China, such as current society guidelines on HCV treatment (ie the standard of treatment), the resource, availability and accessibility of DAA for most CHC patients (eg, CFDA approved, not approved, but accessible to the patients), the treatment costs, providers' knowledge and experiences, and other barriers to promote DAA treatment in China.

Response: We agree with the reviewer that defining the current issues in the treatment of HCV in China would help better demonstrate the value of curative HCV therapies. Relevant information on the current landscape of HCV treatment in China has been added in the Introduction (page 7). Presently there are no reliable data to capture how the relative proportions of Chinese patients using DAAs versus interferon-based

therapies have been changing since DAAs became available. Drug accessibility and affordability remain the main barriers to adopting DAA therapies, which are not covered by the National Healthcare Insurance scheme for reimbursement.

3. It is also important to introduce all DAA treatment trial data in China in the text (not just listed in Table 1).

Response: Descriptions of the data from pivotal DAA trials in China have been added in the text of Section 2.1 (pages 10–11).

4. The MS emphasizes the important value of DAA, but focus mainly on Sof-based regimen, making the MS imbalanced to other non-Sof DAA regimens.

Response: We agree with the reviewer that it is important to present a balanced perspective with respect to the different DAA regimens. Changes made to address this issue include:

1) When introducing pivotal DAA trials from China in Section 2.1 (pages 10–11) and Table 1, results have been added for the regimens EBR/GZR and O/P/r + D.

2) When introducing modeling studies that predict the long-term health outcomes of DAAs versus interferon-based treatments in Section 2.1 (page 11) and Table 2, a recent study presented at APASL in February 2019 has been added, which predicted that relative to PR treatment, the pan-genotypic regimens GLE/PIB and SOF/VEL would achieve comparably high reductions in liver sequelae (Ref 57). Furthermore, thanks to the suggestion of another reviewer, a modeling study by Wu *et al.* (Hepatology, December 2018) has been added (Ref 55); this study modeled the HCV disease burden in China from 2004 to 2050. The model used the conservative estimate of 90% for the efficacy of "DAA treatment" without distinguishing the individual regimens, and predicted that DAA treatment for all patients with a METAVIR fibrosis score ≥ F3 or universal adoption of DAAs regardless of fibrosis status would significantly reduce

the future HCV disease burden in China compared to a pre-DAA scenario that assumes continued PR usage without DAAs.

3) When discussing cost-effectiveness analyses from China in Section 3.2 (pages 18–19), the text has been modified to make it clear that all of the DAA regimens currently available in China have been predicted in some studies as cost-saving or cost-effective compared to PR treatment. Two recently published cost-effectiveness studies have been added, one reporting comparisons of O/P/r + D and SOF + RBV versus PR (Ref 98), and the other, EBR/GZR versus DCV + ASV (Ref 99). A Taiwanese study (Ref 100) has also been added, which evaluated the costs per SVR for PR treatment, and using EBR/GZR as an example, suggested that highly efficacious DAAs can offer comparable costs per SVR for patients who are difficult to treat with PR.

5. This seems a MS drafted by the medical writers funded by Gilead. In Author contributions' statement, they declare all the authors "contributed equally". It is important to detail the role of each individual author, especially those Gilead's employees. Did all coauthors participate in MS drafting, or by medical writers?

Response: All the authors participated in discussion at the study conception stage to decide on the outline for the manuscript, and all the authors participated in critically reviewing and revising the manuscript draft. The medical writers drafted the manuscript based on the outline and edited the draft according to the input and instructions from the authors. The authors who are Gilead employees additionally provided communications support to liaise with the other authors to organize the initial conception discussion and the subsequent draft review process. The component of "drafting" has been removed from the Author contributions statement accordingly.

6. The MS spends a great deal of time talking about cost-effectiveness by comparing Sof-based vs PR regimen. However, did not even mention another available pan-genotypic regimen, which could be even more cost-effective.

Response: Based on the current availability of cost-effectiveness data from China, majority of the modeling studies compared genotype-specific DAA regimens with PR (page 18). Concerning pan-genotypic regimens, one study (Ref 98, added during revision) predicted SOF + RBV to be cost-effective and cost-saving compared with PR in GT2/3 and GT6 patients respectively. In the study that compared multiple DAA regimens and PR (Ref 56), the pan-genotypic regimen GLE/PIB was not included as it was not yet approved in China at the time of the study. A more recent study (Ref 57, added during revision) predicted that GLE/PIB would achieve comparable percentage reductions in adverse liver sequelae as SOF/VEL, although no cost-effectiveness study has been published that directly compares SOF/VEL and GLE/PIB.

7. The MS spends too much time to compare PR data with DAA data, but PR regimens are considered the retired regimens, no longer used in many countries.

Response: Unlike in more developed countries, DAAs only started to be approved in China since 2017. Presently despite the improved drug availability, DAAs are much less affordable than traditional, interferon-based treatment in China, limiting the access by patients with low income and those in rural/less developed areas. We believe that for Chinese policy makers in public health and health technology assessment, all-round comparisons of DAAs and PR would still be highly relevant and informative as they consider which treatment options would bring more value to patients and society and therefore should be allocated with more of the finite public health resources available. This has been clarified through text added in the Introduction (page 7, in response to comment point 2 above) and in Section 3.2 (page 18).

8. Some portion is presented based on speculation, rather data driven (at least no references included). Such as "The resulting healthcare expenditures, as well as reduction in quality of life and loss of work productivity among the Chinese CHC

population, are expected to have wide-ranging economic and societal implications.", in page 6. Ref 17 is not accessible?

Response: The sentence quoted by the reviewer is an overarching statement in the Introduction, which will be substantiated through the discussion in subsequent sections. Data are introduced where available from modeling studies that sought to predict the economic and societal impact of HCV infection in China: in Section 3.1 (pages 15–16) and Figure 3, data are presented for the predicted medical cost due to HCV-related liver disease progression; in Section 3.1 (page 16) and Figure 4C, data are presented on the monetized productivity loss among Chinese GT1 HCV patients in the absence of treatment.

The speculative wording at the end of Section 2.1 has been removed, as the preceding paragraph (page 11) now presents data from multiple Chinese modeling studies on the predicted reductions in HCV-related liver sequelae. The speculative wording at the end of Section 2.2 has been removed, as indicated in the response to comment point 9 below.

We have tested the URL provided in Ref 17 (now numbered Ref 12 in the revised draft), and it links to the pdf version of the National Essential Drug List (2018) of China. The document is published in Chinese.

9. HCV-related EHMs can be divided to "related and possibly related". The MS described all them so detailed, but indifferently. It is also important to include data on which EHMs are more commonly seen in CHC patients in China or Asia. Additional most references are based PR, but not DAA.

Response: Text in Section 2.2 (page 12) has been modified to reflect the differential levels of association of EHMs with HCV infection.

Due to a lack of published evidence in the literature, it was not possible to discuss which EHMs are more commonly seen in Chinese CHC patients. A recent Chinese review by Wang *et al.* (Ref 61, added during revision) flags the lack of clinical data on HCV-related EHMs in China, suggesting that this may be because patients presenting with EHMs are scattered in different hospital departments when seeking treatment, and are thus difficult to study without inter-departmental collaborations.

Since PR has been in use for much longer than DAAs for treating HCV, a large amount of data has been accumulated on the effect of PR-mediated SVR on EHMs, whereas such data for DAAs are only emerging. Thus, the content of Section 2.2 is subject to data availability in the literature. The text at the end of Section 2.2 (page 13) has been rephrased to clarify that while further research is needed to deepen the understanding of the impact of DAAs on EHMs, emerging data suggest DAA-mediated HCV cure can confer the additional health benefit of alleviating EHMs. Detailed existing data on the effect of DAAs on EHMs can be found in other reviews (Refs 66–67).

10. The MS mentioned harm reduction so briefly. It is valuable if this is further discussed to prevent recurrent HCV infection

Response: A paragraph has been added in Section 5.1 (page 26) to discuss the importance of harm reduction and prevention of HCV reinfection.

11. As this MS focuses on The Clinical, Economic, Societal, and Patient Value of DAA treatment, it is valuable to statistically predict the exact changes or values after DAA application

Response: As we try to explain with the opening paragraph of Section 3 (page 15), Figure 2, and the first paragraph in Section 5.2 (pages 26–27; previously in Conclusion), a holistic assessment of the "value" of certain treatment options entails numerous aspects, not all of which are currently captured in models/value assessment systems that generate monetized/numerical outputs. Where possible, we have reviewed and

introduced published studies that reported such "statistical predictions" in different aspects (disease burden, long-term health outcome, cost-effectiveness, and work productivity), whereas to conduct additional modeling analyses would be beyond the scope of this review.

12. Needs assessment in China in this field.

Response: Please kindly refer to the response to comment point 2 above.

13. For all figures referenced in literature, a permit of use should to be obtained and stated in the legends.

Response: For copyrighted graphic materials taken from published manuscripts (Figure 1, and Figures 4A–B), we will request permission for reuse if this manuscript is accepted for publication. Figure 2 is an original figure; Figure 3 and Figure 4C were generated using numerical data reported in the references cited. The figure legends have been updated to reflect the aforementioned information.

Minor comments:

14. In China, the first DAA regimens were approved in 2017; however, as of 2018, PR "therapy is still used extensively in many areas[5]." These needs to be more detailed, especially why PR is still used, MS education, DAA availability, or funding coverage issue?

Response: In the process of addressing comment point 2 above, this sentence has been removed from the text, and relevant background information on the current status of HCV treatment in China has been added in the Introduction (page 7).

Response:

15. "systemic nature of CHC", should be "besides liver, HCV infection may involve other organ system".

Response: In the process of addressing comment point 2 above, the text in the Introduction was modified, resulting in the sentence mentioning the "systemic nature of CHC" being removed.

16. "25.5 percentage points" should be "25.5%" in p9?

Response: The study concerned (Ref 31) reported that the cumulative risk of HCC was 20.1% for cirrhotic patients who achieved SVR, and 45.6% for cirrhotic patients without SVR. We believe that "percentage point" is a legitimate unit used to express the arithmetic difference between two percentages, thus the difference between 45.6% to 20.1% has been expressed as 25.5 percentage points.

17. "Considering these data, it is reasonable to anticipate that a national roll-out of DAA treatment in China would significantly alleviate HCV-related disease burden by averting hundreds of thousands of cases of cirrhosis, HCC, and death." should be "a national application of DAA" in p10?

Response: In the process of addressing comment point 8 above, this sentence has been removed from the text.

18. "(vs no SVR, OR 0.44, 95% CI [0.28, 0.67])" should be "(vs no SVR, OR 0.44, 95% CI [0.28-0.67])," in p 11?

Response: The presentation of the 95% CI has been changed to [0.28–0.67] (page 12).

19. "China sees substantial regional variation in risk factors for HCV infection" should be "Substantial regional variation in risk factors for HCV infection exists in China", in p12?

Response: This sentence has been changed to "There is substantial regional variation in risk factors for HCV infection in China" (page 13).

20. The authors stated "In China, studies on PROs in HCV patients have been scarce." But use discussed too much related issue by referencing non-Asian data.

Response: The sentence quoted by the reviewer appears in Section 4.1 (page 22), which discusses the HCV disease burden in China as reflected in PRO data. Despite the scarcity of PRO data in China, we tried as far as possible to synthesize the information available in the literature and introduced four studies from China reporting PRO/quality of life data.

21. "this papers." should be this paper." In p 25

Response: This has been corrected to "this paper".

22. Suggest move the ref list in table 1 from left to most right. Table 1 data should be well included to the text to make the MS balanced.

Response: The reference list in Table 1 has been moved to the rightmost column. Description of the data contained in Table 1 has been added to the text in Section 2.1 (pages 10–11), as mentioned in the response to comment point 3 above.

23. Conclusion is too long, usually one para.

Response: The final sections of the manuscript have been restructured (for details please refer to the response to comment point 24 below) such that the Conclusion section now consists of one paragraph only.

24. Would suggest including a session on the current challenge and future research and commitment direction.

Response: A new section, Section 5 (pages 25–27), has been added as suggested by the reviewer. Section 5.1 discusses some of the technical challenges and important issues

in HCV management, mostly suggested by various reviewers for addition into the manuscript. Section 5.2 contains some suggestions concerning the future development of China's value assessment research and public health policies for the management of HCV, which had been in the Conclusion of the previous draft.

25. The MS seems too long, should be shorten dramatically (defer to staff editor).

Response: Since the Journal of Hepatology does not stipulate a word limit for review articles, we have taken the liberty of developing this manuscript to its current length, in the hope of thoroughly discussing the multi-faceted topic of the value of curative HCV therapies.

Reviewer 02528812:

This review summarizes the value of hepatitis C treatment in China from clinical, economic, societal, and patient experience perspective. The study is well written and organized. I have a few comments.

Response: We thank the reviewer for reviewing and providing comments on this manuscript.

Authors should include the following: 1) The emergence of HCV resistance-associated variants (RAVs), which occur naturally during the replication of the virus and select under the pressure of DAAs and finally results in treatment failure. 2) Strategic planning to avoid the emergence of RAVs.

Response: A paragraph has been added in Section 5.1 (pages 25–26) to highlight the issue of resistance-associated substitutions and its implications for the use of DAA therapies.

[Authors should include the following:] 3) A list of prophylactic vaccine candidates against HCV infection. 4) Mechanisms of vaccines failures: what we learned from failures.

Response: A paragraph has been added in Section 5.1 (page 26) regarding prophylactic HCV vaccines. Since the focus of this manuscript is on curative anti-HCV therapies, we kept this discussion on prophylactic vaccines brief, and pointed readers to other review articles that provide further information on the research progress in HCV vaccines (Refs 136–137).

[Authors should include the following:] 5) Social and economic side of HCV elimination.

Response: We agree with the reviewer that HCV elimination, being a strategic goal championed by the WHO, is of great importance. The introduction of DAAs represents opportunities for significantly improving HCV treatment in China, but with the huge patient population, elimination would unlikely be achieved in the short term. Thus, in this manuscript we focused on the social and economic impact of DAAs as curative therapies, instead of exploring the social and economic considerations related to HCV elimination. Wu *et al.* (Ref 55, added during revision) modeled the impact of two DAA accessibility scenarios with risk-based screening strategy on the projected HCV disease burden in China, and suggested that in addition to DAA coverage, expanded screening may be a necessary step for China to control its future HCV disease burden.

Reviewer 03475479:

Authors described about the clinical, economic, societal effect of anti-viral treatment for chronic HCV infection in China. This review is well-addressed and well-written, and informative for clinicians. In China, HBV-coinfection might be frequently found. Authors should mention about HBV-coinfection (e.g. prevalence, the effect or the caution in anti-viral treatment).

Response: We thank the reviewer for these comments. As per the reviewer's suggestion, a paragraph has been added in Section 5.1 (page 25) to highlight the

prevalence of HBV coinfection and the monitoring needs for HBV/HCV-coinfected patients in China.

Reviewer 00503849:

The manuscript was well written which can provide useful information to the readers. I recommend publishing this manuscript.

Response: We thank the reviewer for the positive feedback on this manuscript.

Reviewer 03488192:

Interesting and valuable article by Xie Q et al., on the Clinical, Economic, Societal, and Patient consequences of HCV Cure in China. It presents a good introduction and extensive review on HCV cure-related topics in China. The burden of liver disease in China is an important subject of great interest both for the journal and for the international community of hepatologists-gastroenterologists. It follows a trend, with increasing numbers of articles, presenting and informing about the advances in the management of HCV infection in that great nation with an important number of patients with HCV infection representing 6.6 % of the HCV positive world population (Wang et al. Hepatology 2014). This reviewer has read and agrees with all the information presented. However, there are two important aspects that should be included and reviewed.

Response: We thank the reviewer for both the positive and constructive comments on this manuscript.

An important point is that when writing about some predictive modeling in China, specifically refs. 52, 53 and 85, they cite abstracts which do not have all the information to read about the methodology, to check the results and get a thorough opinion. I suggest the authors obtain the full articles or substitute them with complete articles. Unfortunately the authors rely importantly on these type of sources.

Response: For modeling studies in China/Asia, references to full articles have been added as far as possible, including new references for two cost-effectiveness modeling studies (Refs 98–99), one real-world observational study with cost-effectiveness analysis (Ref 100), and one budget impact study (Ref 102) in Section 3.2 (pages 18–19). The studies in the original references 53 and 85 highlighted by the reviewer, and a few other studies included in the manuscript, have only been presented as posters/oral presentations at research conferences; nonetheless, we consider it worthwhile to introduce these studies to readers. We understand that readers, like the reviewer, may be interested in finding out more about the methodology and results of these studies, and would like to suggest that they consider contacting the authors of the original posters/presentations for such information. (The original reference 52 has been removed due to redundancy with the original reference 53.)

On the other hand, there is/are recent articles using some predictive models about the prevalence and mortality related to HCV infection in China which should be included (Wu…Li, et al, Hepatology 2018, e publication). In that respect I think that the authors could use that information to do the cost-analysis of treatment HCV with DDAs in terms of projected prevalence on the one hand and the benefits of DDAs treatment on reduced mortality on the other. Those results could also be included in Figure 2. An important part of the analysis of the value of using DAAs en HCV treatment which is also related to the treatment of advanced cirrhosis and HCC is transplantation, which is not included in the review but is a piece of information which will complete the analysis i.e. how many liver transplants will not be needed or performed after the general use of DDAs (to be included also in Figure 2).

Response: We thank the reviewer for pointing us to Wu *et al.* 2018, as we found it a very informative study to enrich the content of this manuscript. The following changes have been made according to the reviewer's recommendations:

1) From Wu *et al.* 2018, the predicted HCV prevalence and mortality, as well as the predicted effects of DAA versus PR treatment on reducing the HCV disease burden

(including reduction in liver transplants) in China have been added in Section 2.1 (page 11).

2) A column has been added to Table 2 to report the predicted percentage reductions in liver transplant using DAA regimens versus PR treatment.

3) Concerning the cost analysis suggested by the reviewer: the value impact of mortality is complex as, on the one hand, it translates into reduced medical costs due to patients no longer receiving treatment, while on the other hand, mortality would lead to productivity loss and hence monetized value loss for society. Conducting additional modeling analyses to incorporate these value aspects is beyond the scope of this manuscript, which only seeks to review published cost-saving and cost-effectiveness data available in the literature. Nevertheless, we have added to Figure 2 the relative percentage reductions in decompensated cirrhosis, hepatocellular carcinoma, and liver transplant of DAA treatment versus PR treatment as predicted in Wu *et al.* 2018.

Finally, the word "Curing" in the title looks somehow peculiar although it can be used. A first attempt to find similar titles in PubMed, showed that it is not in the main key word descriptors list and I found it only as "HIV cure". I suggest changing the word for something which is more readily found with most search browsers.

Response: We have changed the title to "HCV Cure with DAAs: …", with "HCV cure" following a similar pattern to "HIV cure" as mentioned by the reviewer.

Reviewer 00503536:

The review written by Xie et al. summarizes the treatment efficacy for HCV infection with the economic and societal burden of chronic hepatitis C. The review is comprehensive and well written. However, there are some misspelling and a concern that need to be addressed. Minor point 1. The efficacy of DAA is different according to the genotype of HCV. Especially, the efficacy is lower in patients with

HCV genotype 3 than those with genotype 1 or 2. Therefore, the data should be separated.

Response: We thank the reviewer for the comments. The revised manuscript has been carefully proofread and corrected for any misspellings found. As per the reviewer's suggestion, the efficacy data have been reported separately for different HCV genotypes in Table 1 and described accordingly in the text of Section 2.1. Furthermore, a paragraph has been added in Section 5.1 (page 25) to highlight that with existing pan-genotypic DAA regimens, patients with GT3 HCV tend to be more difficult to treat than those with other genotypes.