

## ROUND 1

March 16, 2021

To Dr. Lian-Sheng Ma, Company Editor-in-Chief,

We would like to thank the editor and reviewers for taking the time to carefully review the re-submission of our work entitled “*A New Hope for Hepatitis C Virus: Summary of Global Epidemiologic Changes and Novel Innovations Over 20 Years*” (Manuscript NO.: 63529). We have clarified the issues raised by the reviewers and described the revisions made to the manuscript. We hope the manuscript in its revised form will be of high interest to the audience of *the World Journal of Gastroenterology*. We have summarized our response to the reviewers below.

### Reviewer 1

*First, this manuscript mainly describes the epidemiology and new hope of hepatitis C in the world in recent 20 years. And put forward the unique insight that fair DAAs treatment opportunities can reduce the mortality of hepatitis C. Second, the quality and importance of this manuscript is very good. Before and after the use of DAAs, the mortality rate of hepatitis C has changed significantly. However pharmaceutical costs limit equitable access to healthcare. Based on this, the author proposed the essential agenda items include prioritization of access to DAAs therapies in addition to transparent negotiations with the pharmaceutical industry to consider the compassionate release of medications to promote equitable division of care. Third, this manuscript finally pointed out the future direction should be devoted to the prioritization of HCV infection in order to increase its importance on the international agenda, especially in the World Health Organization. Additionally, pharmaceutical companies need to consider providing compassionate release of medications to promote equitable healthcare worldwide, especially given the highest disease burden within low- and middle-income countries.*

### Reply:

We kindly thank the reviewer for their positive feedback and thorough assessment of the manuscript. We are pleased the objectives and main points of this review have come across clearly to the reader.

### Reviewer 2

*1. The present study is a well-written review on HCV epidemiological changes, new treatments, and inequalities in access to care. The subject has a high priority for publishing, given the inadequate HCV care programs worldwide and the urgent need for policy change, particularly in low and middle-income regions. Overall, I found the manuscript suitable for publication; however, major revisions are required. The authors need to expand on the feasible ways for scaling up HCV elimination efforts in resource-limited settings. There are many examples of integrated HCV care models such as prison-based programs, community integrated models, or*

*using OAT infrastructure, which could pave the way towards elimination in low and middle-income countries.*

**Reply:**

We are pleased with the reviewer's positive assessment of this work. The reviewer brings forward excellent suggestions, specifically the need for further discussion on novel methods for scaling up HCV elimination efforts in resource-limited settings. We have now included a new section entitled, **"Innovative Examples of HCV Elimination Efforts in Resource-Limited Settings"**, which describes the excellent examples of prison-based programs, community-integrated models, and use of OAT infrastructure.

*2. The section "Global epidemiological trends" is mainly presenting epidemiological data from the United States, and its title does not reflect the content. Authors should discuss "global" HCV trends and expand on its epidemiology in different regions.*

**Reply:**

The reviewer provides excellent constructive feedback suggesting further modifications to our Global epidemiologic trends sections. We have removed the epidemiologic data from the US and revised this section to focus more on the global burden of HCV.

*3. There are many hard-to-reach and wordy sentences in the manuscript that need rephrasing. The correct use of punctuations should definitely be considered. Several sentences and paragraphs that have been presented in the body of the manuscript belong to the introduction. In some parts, lack of coherency between paragraphs is sensible. Also, overly detailed discussion together with multiple numbers presented in some paragraphs may make the reader distracted from the main point.*

**Reply:**

We have thoroughly reviewed the manuscript to ensure the correct use of punctuation and revised our writing to improve flow and reduce the use of run-on sentences and areas seeming unclear or "hard-to-reach". We have also moved the important sections identified by the reviewer from the body of the manuscript to the introduction.

*4. Abstract: "To reduce the burden of disease worldwide.... division of care.": This sentence is hard to reach, consider splitting into two sentences*

**Reply:**

We have revised this sentence in our abstract as per the reviewer's recommendation.

*5. Global epidemiological trends: This section needs major revisions. Authors may remove some numbers and estimates from the US and more expand on the global epidemiology and trends in different countries. Otherwise, the title should change.*

**Reply:**

We have revised this section as per the reviewer's recommendation. We have removed the previously cited numbers and estimates from the US to have instead focused on global trends.

*6. Global epidemiological trends: 1<sup>st</sup> paragraph: This paragraph can be moved to the introduction.*

**Reply:**

We have revised the first paragraph of this section to address the specific section aims.

*7. "third world countries" is an outdated and offensive term for a developing country; it should be substituted by "low and middle-income countries".*

**Reply:**

We thank the reviewer for identifying this inappropriate term. We have replaced "third world countries" with "low and middle-income countries".

*8. Authors should strictly avoid using stigmatizing words like "intravenous drug users". This term should be substituted by "people who inject drugs" (PWID) throughout the manuscript.*

**Reply:**

We have substituted all instances of "intravenous drug use" with "people who inject drugs".

*9. Italy is not an Asian country; the sentence should be rewritten.*

**Reply:**

We have revised this section to read instead, "Evaluation of global epidemiologic trends with a focus on regional prevalence identifies Asian and African countries to have the highest prevalence of cases, with Egypt (18-22%) and Pakistan (4.9%) exhibiting the highest rate of chronic infection. Among high-income countries, Italy (2.5-10%) remains the most impacted, with as high as 10% of its population reporting chronic HCV infection."

*10. Consider changing "unclean" needles to "contaminated" needles.*

**Reply:**

We have revised "unclean" to "contaminated."

*11. "Treatment of schistosomiasis, an endemic parasitic infection in Egypt...": This sentence does not seem consistent with the rest of the paragraph that presents some estimations from the US.*

**Reply:**

We have removed this sentence.

*12. "intravenous drug users" should be substituted by "PWID".*

**Reply:**

We have removed the term "injecting drug user" from this paper, replacing all instances with people who inject drugs (PWID).

ple who inject drugs.

**13.** *“Following exposure, the virus incubates ... at 20-30 years”: I believe this section also belongs to the introduction.*

**Reply:**

We agree this sentence should be moved to a more appropriate section. We have instead moved this sentence to the section on HCV virology and Genomic Sequencing.

**14.** *“The annual percentage change ... per 100,000 persons in 2018.”: I would simplify this paragraph. It has too many numbers and may be hard to reach for the general audience*

**Reply:**

We have removed this sentence from this section.

**15.** *HCV Virology and Genomic Sequencing: - The word “flavivirus” should be rewritten*

**Reply:**

We have removed the word from this sentence.

**16.** *“This positive-sense, single-stranded virus is demonstrated to be 9,600 ribonucleotides containing a poly(A) tail at the 3' end.”: I would remove these details*

**Reply:**

We have removed this sentence.

**17.** *“Following the isolation of this strain, Houghton's team were able to develop ... including Elisa immunoassays (EIA).”: It may be interesting to add some information about the 2020 Nobel prize in physiology or medicine which is awarded to this team, and its reason.*

**Reply:**

We have now highlighted Houghton's team's incredible recognition with the 2020 Nobel prize in medicine and physiology.

**18.** *“Genomic isolates of ... is part explained by.”: the term “part” should change to partly*

**Reply:**

We have revised the word “part” to “partly.”

**19.** *Out with the old, in with new - Novel therapeutics in the treatment of HCV: This subject is very interesting and more issues related to new DAAs can be discussed here, like their availability in different regions of the world, their efficacy on people with ongoing injection drug use and other high-risk populations, etc. This section needs to be more expanded, unlike the other sections that are already discussed in details.*

**Reply:**

We have made extensive revisions to this section to include additional information about DAAs. In our discussion of DAAs, we have now included a brief introduction to pangenotypic drug selection and the impact of drug-drug interactions. We have also included a new paragraph detailing global access issues. Please refer to the section entitled “**Out with the old, in with new – Novel therapeutics in the treatment of HCV**” for these changes.

**20.** *“Unless contraindicated, all patients with chronic HCV infection should be offered treatment.”: Approach to some probable contraindications can be mentioned here like patients with cirrhosis and HBV/HCV co-infected individuals, or administration in pregnancy*

**Reply:**

We have now included a new paragraph outlining contraindications to therapy and an approach to special populations, including pregnancy and patients with co-infection. Please refer to paragraph 5 of the section entitled “**Out with the old, in with new – Novel therapeutics in the treatment of HCV.**”

**21.** *Liver Transplantation in the Context of Hepatitis C Virus: “Between 2012 and 2015, HCV ... to HCV-related liver disease.”: These two sentences can be combined.*

**Reply:**

We have combined these sentences.

**22.** *“Patients affected by HCV-related liver disease ... is warranted in these populations.”: I would rather remove this paragraph. The section is mainly about DAAs and liver transplantation, so touching on some post-transplant complications does not seem necessary here.*

**Reply:**

We have removed this paragraph.

**23.** *“In 2007, a survey of 702 patients ... had undergone kidney transplantation.”: This is an outdated study. I suggest removing it*

**Reply:**

We have removed this sentence.

**24.** *“Approximately half (53.9%) patients required... and to declare bankruptcy.”: The sentence should be rephrased and summarized*

**Reply:**

We revised this sentence; it now reads, “On average, the out-of-pocket expense for liver transplantation was noted to be \$476.60 USD. Approximately half (53.9%) patients required personal savings and credit (25%) to offset the costs. When compared to patients undergoing kidney transplantation, liver recipients were more likely to rely on alternative sources of funds, including personal loans from friends or family members, retirement funds, and community-based fundraising campaigns.”

**25. Global Inequities in Access to Care: The Pharmaceutical Dilemma:** - Due to the limitations in public health funding and infrastructure and shortage of specialized clinicians in low and middle-income countries, integrated HCV care models can be a good option for scaling up HCV programs. Some examples of these models are prison-based test-and-treat programs conducted by the prison healthcare staff (general practitioners and nurses), community integrated programs conducted by primary healthcare providers, or using OAT infrastructure. Authors need to discuss these possible solutions somewhere in the manuscript. Here are some examples of successful integrated HCV models:

*Overton K, et al. Outcomes of a nurse-led model of care for hepatitis C assessment and treatment with direct-acting antivirals in the custodial setting. Int J Drug Policy. 2019*

*Hariri S, et al. Continuum of hepatitis C care cascade in prison and following release in the direct-acting antivirals era. Harm Reduct J. 2020*

*Read P, et al. Delivering direct acting antiviral therapy for hepatitis C to highly marginalised and current drug injecting populations in a targeted primary health care setting. Int J Drug Policy. 2017*

**Reply:**

The reviewer brings forward an excellent suggestion, specifically the need for further discussion on novel methods for scaling up HCV elimination efforts in resource-limited settings. We have now included a new section entitled, “**Innovative Examples of HCV Elimination Efforts in Resource-Limited Settings,**” which describes the excellent examples of prison-based programs, community-integrated models, and use of OAT infrastructure.

**26.** “The prioritization of other ... including cirrhosis and HCC.”: The sentence is unclear and should be rewritten.

**Reply:**

This sentence has been revised and now reads, “The prioritization of other infectious diseases above HCV leads to considerable diversion of resources away from targeting the important health outcomes resulting from hepatitis infection, including cirrhosis and HCC.”

**27.** “According to the WHO....2017.”: This sentence is repetitive; authors have already mentioned this in the introduction.

**Reply:**

We have removed this sentence from the manuscript.

**28.** “Amongst these, only 13.1 million individuals aware of their diagnosis.”: The verb is missing

**Reply:**

This sentence has been removed.

**29.** *“While middle- to high-income ... nevertheless substantial.”: Consider the correct use of punctuation or rephrasing*

**Reply:**

We have revised this sentence; it now reads, “Many countries will prioritize curative treatment for HCV with DAAs to mitigate downstream costs associated with end-stage liver disease. Irrespective of savings, the total cost of DAAs is substantial.”

**30.** *“Current estimates place DAAs in the highest cost category.”: Well, this sentence is not completely true in the global context. In some countries, generic DAAs are available at very low prices. For example, in Iran, a locally manufactured fixed-dose combination of Sofosbuvir/Daclatasvir is widely available (which costs nearly \$50-65 USD for a 12-week regimen). In such countries, the main problem is lack of national HCV test-and-treat programs among high-risk groups. Here is an example of a comprehensive community-based HCV care model in Egypt: Shiha G, et al. An educate, test and treat model towards elimination of hepatitis C infection in Egypt: Feasibility and effectiveness in 73 villages. J Hepatol. 2020*

**Reply:**

We have revised our section entitled “**Global Inequities in Access to Care: The Pharmaceutical Dilemma**” to discuss the important issues raised by this reviewer. We have now touched on topics related to local manufacturing initiatives, and the impact of such initiatives on DAA cost and access. Please refer to paragraph 5 of this section. We elected to include the discussion of the novel comprehensive community-based HCV care model described by Shiha et al. (2020) in our new section entitled, “**Innovative Examples of HCV Elimination Efforts in Resource-Limited Settings.**”

**31.** *“Thus, inequitable access ... health recommendations.”: It is a hard-to-reach sentence, consider rephrasing*

**Reply:**

We have revised this sentence; it now reads, “Variability in access to treatment is a serious problem within the US, driven largely by limitations within the health infrastructure. Disproportionate allocation of resources has led insurers to enact restrictions on the delivery of HCV medications.”

**32.** *Future Directions: Integrated HCV care models can be mentioned here as a feasible and effective strategy*

**Reply:**

We have now included a new section entitled, “**Innovative Examples of HCV Elimination Efforts in Resource-Limited Settings,**” which describes the excellent examples of prison-based programs, community-integrated models, and use of OAT infrastructure.

33. *“Requirements for ... (glomerular filtration rate).”: Sentence should be rephrased*

**Reply:**

We have revised this sentence. The paragraph now reads, “Ancillary costs contributing to the safe and effective delivery of HCV care are undoubtedly expensive. These expenses are largely driven by the costs associated with healthcare personnel, as well as diagnostic and laboratory testing.

Provider experience (specialized training in hepatology, infectious disease, general internal medicine), technology for fibrotic staging, as well as baseline laboratory measures including transaminase levels, HCV RNA level, HCV genotype, measures of synthetic liver function (glucose, platelets, albumin), and current renal function account for the bulk of health delivery expenses.”

34. *“There is even less ... different insurers or plans.”: Sentence should be rephrased*

**Reply:**

We have removed this sentence from the manuscript.

**Reviewer 3**

1. *This review article provides a good summary of the progress made in HCV to the DAA era and then discusses the potential for global elimination and barriers in achieving this - it needs further development to address the following areas :- Major Structurally - elements of the global epidemiological trends would be better placed in the HCV virology section (transmission, viral course etc)*

**Reply:**

We thank the reviewer for their constructive evaluation of the manuscript. We agree with the reviewer, multiple paragraphs of the global epidemiologic trends section would fit better within the HCV virology section. We have moved these accordingly.

2. *Further discussion regarding determination of SVR at 12/52 as indicating viral cure would be of value as this has changed over time.*

**Reply:**

We have included a new paragraph discussing the determination of sustained viral response at 12 weeks. Please refer to paragraph 1 of the section entitled, **“Out with the old, in with new – Novel therapeutics in the treatment of HCV.”**

3. *Some discussion regarding HCC risk and DAA therapy should be included given the controversy of this topic at the time*

**Reply:**



Please refer to the last paragraph of the “**Out with the old, in with new – Novel therapeutics in the treatment of HCV**” section, where we have included a discussion regarding HCC risk and DAA therapy.

*4. A discussion regarding DDIs and determining optimal pan genotypic selection would be of interest*

**Reply:**

In our discussion of DAAs, we have now included a brief introduction to pangenotypic drug selection and the impact of DDIs. Please refer to paragraph 3 of the section entitled, “**Out with the old, in with new – Novel therapeutics in the treatment of HCV,**” for the newly added paragraph regarding pangenotypic therapies, including references to some of the groundbreaking trials. Please refer to paragraph 4 of this section for our new discussion on DDIs observed with DAAs.

*5. When considering global elimination of HCV – there needs to be discussion regarding implementation of effective screening programs targeting at risk populations – there are a number of models that could be proposed that are utilised around the world. Whilst DAAs are effective at treating patients with HCV – for an elimination strategy, one could argue that the development of a vaccine may be of greater benefit in achieving this strategy. This should be discussed in the context of recent developments in HCV vaccine field.*

**Reply:**

We agree with the reviewer; further discussion was needed for novel approaches to elimination, particularly in resource-limited settings. We have included an entirely new section entitled, “**Innovative Examples of HCV Elimination Efforts in Resource-Limited Settings,**” discussing integrated care models used in vulnerable populations, including prison settings and substance use treatment centers. We have also included a section on vaccine development within the last paragraph of the section entitled, “**Out with the old, in with new – Novel therapeutics in the treatment of HCV.**”

*6. Minor Few typos throughout velpatasvir*

**Reply:**

We have revised this grammatical error.

*7. Would revise first sentence of global epidemiological trends section*

**Reply:**

We have revised the first sentence of the global epidemiologic trends section. This now reads, “Evaluation of global epidemiologic trends with a focus on regional prevalence identifies Asian and African countries to have the highest prevalence of cases. Egypt (18-22%) and Pakistan

(4.9%) exhibit the highest rate of chronic infections. Among high-income countries, Italy (2.5-10%) remains the most impacted, with as high as 10% of its population reporting chronic HCV infection.”

**8. Second paragraph page 2 – ‘declaring itself’ is incorrect terminology**

**Reply:**

We have removed this terminology.

**9. Figure 1 may be better presented as a map**

**Reply:**

We thank the reviewer for this excellent suggestion. At this time, we did not have the graphic support to remake this figure into a map. If the editors feel this is an important requirement, we will seek additional editorial support to make this figure.

**10. Table 1 – should include glecaprevir, pibrentasvir and voxilaprevir**

**Reply:**

We have now added these into Table 1.

Science editor

*1. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.*

*2. PMID numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.*

*3. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights.*

*4. Self-cited references: There are 7 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e. those that are most closely related to the topic of the manuscript) and remove all other improper self-citations.*

**Reply to science editor:**

We thank the editor for their thorough review of our manuscript. We have ensured that each of the suggestions have been addressed. We will include a copy of the original figure one in a power point format. We have included the PMID and DOI with all the reference list. We are not reusing any figure from previous work. We have reduced the number of self-citations to ensure less than 10% of references.

We thank the reviewer and editor for their constructive evaluation. We hope we have clarified any of the issues brought forward.

Sincerely,

Dr. Donghee Kim MD, PhD

Division of Gastroenterology and Hepatology  
Stanford University School of Medicine  
300 Pasteur Drive, Stanford, CA 94304

## ROUND 2

To Dr. Lian-Sheng Ma, Company Editor-in-Chief,

We would like to thank the editor and reviewers for taking the time to carefully review the re-submission of our work entitled “*A New Hope for Hepatitis C Virus: Summary of Global Epidemiologic Changes and Novel Innovations Over 20 Years*”(Manuscript NO.: 63529). We have clarified the issues raised by the reviewers and described the revisions made to the manuscript. We hope the manuscript in its revised form will be of high interest to the audience of *the World Journal of Gastroenterology*. We have summarized our response to the reviewers below.

### Reviewer 1

*The authors have addressed my comments and the manuscript is generally better. There are still a few typos throughout the manuscript eg genotypic on page 11 - these need to be addressed.*

### Reply:

We kindly thank the reviewer for their positive feedback and thorough assessment of the manuscript. We have revised the manuscript to correct the grammatical typo on page 11. We have also thoroughly reviewed the manuscript for any additional grammatic errors.

### Reviewer 2

*The revised manuscript is much improved and is suitable for publication.*

**Reply:**

We are pleased with the reviewer's positive assessment of this work.

We thank the reviewers for their constructive feedback and careful evaluation of the manuscript in its revised form. We hope we have clarified any of the issues brought forward.

Sincerely,

Dr. Donghee Kim MD, PhD

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