Dear Editor,

Thank you for your kind consideration of our manuscript (Manuscript NO.: 66746, Retrospective Study) entitled " A care cascade of recently acquired HCV infection among people living with HIV at a university hospital in Taiwan" by Huang MH, et al. The manuscript has been substantially revised according to the suggestions of the Editor and Reviewers. The revision made is highlighted in yellow in the text. We appreciate the kindness and time of the Editor and Reviewers in helping review the manuscript to improve the readability. Enclosed are point-by-point responses addressing each of the concerns raised by the Editor and Reviewers. All authors have reviewed and agreed to the submission of the revised manuscript.

The revisions made are summarized in brief as follows.

1. We have modified the “Core Tip” and “Introduction” as suggested by reviewer#1.
2. We have added the types of antiviral regimens used in treated patients as recommended by reviewer#1.
3. We have modified Table 2 to show the rate of each step of care cascade proceeding to the next step as suggested by reviewer#1.
4. The “Article Highlights” section is added at the end of the main text in the revised manuscript.

We hope that the manuscript is now acceptable for publication. Please do not hesitate to contact me if there are any questions.

Thank you again.

Sincerely yours,

Chien-Ching Hung, MD, PhD

Department of Internal Medicine

National Taiwan University Hospital

E-mail: hcc0401@ntu.edu.tw

Responses to the Reviewers

We would like to thank the reviewer for the extensive assessment of our manuscript, and for the important and helpful comments and suggestions provided. We have taken all the remarks into account, in a manner that is described in detail below together with our answers to certain comments.

Summary of Major Portions of Revision

1. We have modified the “Core Tip” and “Introduction” as suggested by reviewer#1.
2. We have added the types of antiviral regimens used in treated patients as recommended by reviewer#1.
3. We have modified Table 2 to show the rate of each step of care cascade proceeding to the next step as suggested by reviewer#1.
4. The “Article Highlights” section is added at the end of the main text in the revised manuscript.

Comments from Reviewer #1

Comment 1: The Core Tip should be reinforced to present the important findings of the analysis.

Response: We thank the reviewer for the suggestion. We have modified the Core Tip (Lines 27-29, Page 4 and Lines 1-5, Page 5) as follows:

We examined the HCV care cascade among people living with HIV who acquired incident HCV infections at a university hospital in Taiwan between 2011 and 2018. We observed high rates of linkage to HCV care and retention in care in both interferon (IFN, 2011 to 2016) and direct-acting antiviral (DAA, 2017 to 2018) eras. The rate of referral to treatment assessment had increased from the IFN era to the DAA era. Moreover, the duration of HCV viremia was markedly shortened because of early diagnosis and linkage to effective treatment in the DAA era compared to that in the IFN era.

Comment 2: The "Introduction" should be substantially shortened and the initial part of "Materials and methods" in the section "Study population and setting" should be placed in the "Introduction".

Response: We thank the reviewer for the comment. In response to this suggestion,

the “Introduction” section have been largely revised and the main part of “*Study population and setting*” was placed in the “Introduction” section. [Lines 3-13, Page 6] The references 1-4, 7-10, 12, 14-20, 22 are new citations of latest articles in this section, and the citation of other references in the text has been renumbered accordingly. We shorten this section with a total word count reduced from 815 to 430 in this revised manuscript. (Lines 8-29, Page 5 and Lines 1-15, Page 6)

The title “*Data collection*” in “Material and Methods” was modified as “*Study design and Data collection*”[Lines 18, Page 6] in the revised version. The following 2 paragraphs previously in the "*Study population and setting*" are moved to "*Study design and Data collection*" in the revised version: "The study period (2011-2018) spanned two different eras of anti-HCV treatment, from the IFN/RBV era (2011-2016) to the DAA era (2017-2018) before restricted access to HCV treatments was completely lifted in early 2019 " is now moved to Lines 24-26, Page 6; “The study was approved by the Research Ethics Committee of the hospital (registration number: 201605103RINC and 201605128RINC) and informed consent was obtained from all the participants” is moved to Lines 15-17, Page 7.

Comment 3: According to Figure 1. the SVR achieved by patients treated with IFN was surprisingly high and reached 91.6% in the population including 37% of individuals infected with difficult-to-treat GT1a and 1b. Could you provide an explanation for so high efficacy?

Response: We thank the reviewer for the query. According to previous prospective study among people living with HIV in Taiwan, the SVR rate after peginterferon plus ribavirin was 83% in patient with acute HCV infection and 72% in those with chronic HCV infection[1]. In our study, among the 176 patients who acquired incident HCV infection between 2011 and 2016 (IFN era), 71 received peginterferon plus ribavirin, the median time from detection of positive anti-HCV to treatment initiation was 80 days (interquartile range 46 - 212); 61 (85.9%) patients achieved SVR at 24 weeks post-treatment, which is similar to that reported in the aforementioned study by Liu CH[1]. The study by Liu CH is cited in this revised manuscript (Ref. 22). 60 patients who acquired HCV infection in the IFN era delayed antiviral therapy, and subsequently received interferon-free direct-acting antivirals (DAAs), in whom 59 (98.3%) achieved SVR12; therefore, the overall SVR rate to IFN/RBV and DAA in combination of our cohort was 91.6%.

Reference 1: **Liu CH**, *et al*. Peginterferon plus Ribavirin for HIV-infected Patients with Treatment-Naïve Acute or Chronic HCV Infection in Taiwan: A Prospective Cohort Study. *Sci Rep* 2015;**5**:17410 [PMID: 26616669 DOI: 10.1038/srep17410]

Comment 4: I suggest including in the manuscript the data on types of antiviral regimens used in patients treated with both IFN-based and IFN-free options.

Response: We thank the reviewer for the suggestion. In our study population, the IFN-based anti-HCV regimen was PEG-IFN plus weight-based RBV with response-guided treatment duration. During 2016 and 2018, generic versions of IFN-free DAAs (sofosbuvir/velpatasvir) were purchased for treatment because our patients with recently acquired HCV infection did not meet the reimbursement criteria of the National Health Insurance (NHI), which prioritized anti-HCV treatment for individuals with HCV-related advanced liver fibrosis or cirrhosis of the liver. After the restriction was lifted in 2019, sofosbuvir /ledipasvir and glecaprevir/pibrentasvir were reimbursed by NHI for HCV/HIV-coinfected patients. We add the information on anti-HCV treatments used in our patients in the "*Study design and Data collection*" section in "Material and Methods". (Lines 26-29, Page 6)

Comment 5: Please, correct the value of SVR in Table 2, it should be calculated concerning the number of treatment initiated instead of the number of patients positive for anti-HCV.

Response: We thank the reviewer for the comment. We revise Table 2 by indicating the values of percentages for the care cascade that moved from the previous step to the next (Table File. Pages 3-4)

Comment 6: All references, except 22 concerning HCV reinfections in HIV-infected patients, are appropriately selected and used.

Response: We thank the reviewer for the comment. The citation of reference 22 was formerly in the "Study population and setting" section of "Material and Methods". The entire section was revised and moved to the "Introduction" by following the comment of the reviewer (Comment 2); therefore, this reference was removed at the same time. Three new references (references 37, 38, and 39) are cited at the end of Discussion (Line 28, Page 13) to support HCV reinfection among HIV-positive men who have sex with men is not uncommonly observed in several developed countries.

Comments from Reviewer #2

Comment 1: can you mention the causes of increased HCV infection.

Response: We thank the reviewer for the comment. According to the longitudinal cohort study in Taiwan, the incidence of sexually acquired HCV infection among HIV-positive MSM progressively increased since 2000s[1,2]. The similar trends of

increasing incidences of HCV infection among HIV-positive MSM have also been observed in the United States, several European and Asian countries[3-5]. The transmission of HCV could be facilitated by concurrent sexually transmitted infections (eg. syphilis), unprotected anal sex, and serosorting based on HIV serostatus[5,6]. The major risk factor of HCV transmission among MSM is traumatic sexual practices and the use of recreational drugs for "chemsex". The evolving use of injecting "slamming" drugs that results in increased risks of blood contact may have also contributed to the increasing epidemics of HCV infection among MSM[7,8]. Furthermore, because of increasing awareness of the epidemics of incident hepatitis infection in people living with HIV, regular testing for hepatitis markers or HCV RNA as routine screening is also contributory to the increased detection of incident infections. The contributory factors to increased incidence of HCV infection observed are summarized in a recently published review, cited as Ref. 12 in this revised manuscript.

References:

1. **Sun HY**, Chang SY, Yang ZY, Lu CL, Wu H, Yeh CC, Liu WC, Hsieh CY, Hung CC, Chang SC. Recent hepatitis C virus infections in HIV-infected patients in Taiwan: incidence and risk factors. *J Clin Microbiol.* 2012; **50**: 781-787 [PMID: 22189113 DOI: 10.1128/JCM.06014-11]
2. **Ho SY**, Su LH, Sun HY, Huang YS, Chuang YC, Huang MH, Liu WC, Su YC, Lin PH, Chang SY, Hung CC. Trends of recent hepatitis C virus infection among HIV-positive men who have sex with men in Taiwan, 2011-2018. *EClinicalMedicine.* 2020; **24**: 100441 [PMID: 32637905 DOI: 10.1016/j.eclinm.2020.100441]
3. **Chaillon A,** Sun X, Cachay ER, Looney D, Wyles D, Garfein RS, Martin TCS, Jain S, Mehta SR, Smith DM, Little SJ, Martin NK. Primary Incidence of Hepatitis C Virus Infection Among HIV-Infected Men Who Have Sex With Men in San Diego, 2000-2015. *Open Forum Infect Dis*. 2019; **6**: ofz160. [PMID: 31041355 DOI: 10.1093/ofid/ofz160]
4. **van de Laar TJ**, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, van der Meer JT, de Vries HJ, Mulder JW, van Agtmael M, Jurriaans S, Wolthers KC, Coutinho RA. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *J Infect Dis*. 2007; **196**:230-238. [PMID: 17570110 DOI: 10.1086/518796]
5. **Nishijima T**, Shimbo T, Komatsu H, Hamada Y, Gatanaga H, Oka S. Incidence and risk factors for incident Hepatitis C infection among men who have sex with men with HIV-1 infection in a large Urban HIV clinic in Tokyo. *J Acquir Immune Defic Syndr*. 2014; **65**:213-217 [PMID: 24185533 DOI:10.1097/QAI.0000000000000044]
6. **Chan DP**, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus

infection: a review. *Int J Infect Dis*. 2016; **49**: 47-58. [PMID: 27270138 DOI: 10.1016/j.ijid.2016.05.030]

7. **Medland NA**, Chow EP, Bradshaw CS, Read TH, Sasadeusz JJ, Fairley CK. Predictors and incidence of sexually transmitted Hepatitis C virus infection in HIV positive men who have sex with men. *BMC Infect Dis*. 2017; **17**: 185. [PMID: 28253838 DOI: 10.1186/s12879-017-2288-x]
8. **Pufall EL**, Kall M, Shahmanesh M, Nardone A, Gilson R, Delpech V, Ward H; Positive Voices study group. Sexualized drug use ('chemsex') and high-risk sexual behaviours in HIV-positive men who have sex with men. *HIV Med*. 2018; **19**: 261-270. [PMID: 29368440 DOI: 10.1111/hiv.12574]

Comment 2: please mention the degree of freedom for each p value.

Response: We thank the reviewer for allowing us to explain more regarding to the statistic details. The degree of freedom (d.f.) for each p value is shown in the table.

	2011-2018 Total (n=287)	2011 - 2016 IFN era (n=176)	2017 - 2018 DAA era (n=111)		
				d.f.	P value
Antibody detected, n (%)	277 (96.5)	167 (94.9)	110 (99.1)	**N.A**	0.0946
HCV RNA tested, n (%)	270 (94.1)	162 (92.0)	108 (97.3)	**N.A**	0.0759
HCV RNA positivity, n (%)	251 (87.5)	152 (86.4)	99 (89.2)	**1**	0.4815
Referred to treatment assessment, n (%)	226 (78.7)	134 (76.1)	92 (82.9)	**1**	0.1737
Treatment initiated, n (%)	215 (74.9)	131 (74.4)	84 (75.7)	**1**	0.8129
SVR achieved, n (%)	202 (70.4)	120 (68.2)	82 (73.9)	**1**	0.1956
	Interval between each step, median days (IQR)				
Seroconversion to antibody detected	130 (80-295)	179 (87-434)	92 (57-173)	**N.A**	<.0001
Antibody detected to HCV RNA tested	19 (6-81)	21 (6-93)	12 (6-68)	**N.A**	0.1865
HCV RNA tested to treatment assessment	43 (11-181)	26 (7-208)	81 (14-169)	**N.A**	0.2466
Treatment assessment to treatment initiation	36 (21-90)	35 (27-90)	42 (18-84)	**N.A**	0.5466
Duration of viremia	501.50 (324.50 - 945.25)	735.00 (391.25 - 1446.50)	380.50 (273.75 - 553.50)	**250**	<0.0001
Events of STIs during HCV	220	165	55	**1**	<0.0001

viremia					
Incidence rate of STIs during HCV viremia, (per 100-PYFU)	40.97	38.53	50.54	**N.A**	0.0869

Comment 3: lanuage and grammer need polishing

Response: We thank the reviewer for the suggestion. Our manuscript has been professionally edited before submission. The certificate of the English editing service has been uploaded along with our revision.

EDITORIAL OFFICE'S COMMENTS

(1) ***Science editor:***

Comment 1: Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

Response: Thank you for the comment. The approved grant application form is uploaded along with our revision.

Comment 2: Please add the "Article Highlights" section at the end of the main text

Response: Thank you for the comment. The "Article Highlights" section is added at the end of the main text in the revised manuscript (Lines 11-29, Page 14 and Lines 1-21, Page 15).

(2) ***Company editor-in-chief:***

Comment: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you for the comment and we would like to thank you for giving us this opportunity to contribute to the Journal.