

Responses to the Editorial Office's comments

The author must revise the manuscript according to the Editorial Office's comments and suggestions, which listed below:

(1) Science Editor:

1. Scientific quality: The manuscript describes an observational study of the opioid agonist therapy and HCV. The topic is within the scope of the WJG. (1)

Classification: Grade C and Grade D;

2. Summary of the Peer-Review Report: This study addresses a clinically relevant question and results add real-world data about the effectiveness of direct-acting antiviral agents in patients treated with methadone. However, it is unclear whether the population enrolled in this study represents a limited, very selected, part of the population of ex-drug users, suffering from chronic HCV infection. If the authors are able to clarify on the selection process of the studied population, it would be a really significant and valuable contribution to the paper. Moreover, they should better explain which would be the reason of this low treatment rate in the different subgroups. The questions raised by the reviewers should be answered

The questions raised by the reviewers have been answered. Please see the responses to the reviewers below.

3. Format: There is 1 table and 3 figures. A total of 26 references are cited, including 9 references published in the last 3 years. There are 2 self-citations.

2 Language evaluation: Classification: Grade B and Grade B. A language editing certificate issued by BioMed Proofreading LLC was provided. 3

Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, the Institutional Review Board Approval Form, and the informed consent. No academic misconduct was found in the CrossCheck

detection and Bing search. The authors need to fill out the STROBE checklist with page numbers.

Please note that the manuscript includes 2 tables.

After the revision process the final number of references is 28, including 11 references published in the last 3 years and 2 self-citations.

In the submission of the revised manuscript you will see the STROBE checklist with page numbers.

4. Supplementary comments: This is an unsolicited manuscript. The study was performed with 8 financial supports. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.

5. Issues raised:

(1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

We have included all funding agency documents related to the reported grants

(2) I found the authors did not provide the original figures. 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;

In the submission of revised manuscript we provide all the figures in different PowerPoint files to be reprocessed if necessary.

(3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

Please see the new version of the manuscript that includes the “article highlights” in page 19.

Responses to the reviewers

Reviewer #1: 1. Editor's Comments to Author (if any): This study addresses a clinically relevant question and results add real-world data about the effectiveness of direct-acting antiviral agents in patients treated with methadone.

- 1) However, it is unclear whether the population enrolled in this study represents a limited, very selected, part of the population of ex-drug users, suffering from chronic HCV infection. If the authors are able to clarify on the selection process of the studied population, it would be a really significant and valuable contribution to the paper. In particular:
- 132 patients were not enrolled to receive treatment with DAA. What were the main reasons identified for those excluded? (age, comorbidities, etc?) -

We agree with the reviewer. This study represents a proportion of the population of ex-heroin users treated with methadone in an addiction clinic from an urban district of 360.000 people in metropolitan Barcelona, Spain. It is important to note that the selection process of the study population was conducted in the only addiction clinic for the provision of methadone in the area which is good for the internal validity of results. The methadone clinic has appointments with primary care centers for assessing HCV infection and with tertiary hospitals for the provision of HCV treatment which is hospital-based.

The reviewer says that 132 patients were not enrolled to receive treatment with DAAs. In fact, the exact number is 138 patients (249 eligible minus 111 treated) that were enrolled in the study but not treated against HCV during follow-up.

To clarify the selection process of the study population we have modified the paragraph in the Methods section, as follows (pages 5 and 6):

“...This longitudinal study included ex-heroin users enrolled in an OTP between October 2015 and September 2017. The OTP operates in a municipal outpatient clinic specialized in the treatment of SUDs in Badalona (240,000 inhabitants) and Santa Coloma de Gramenet (120,000 inhabitants), Spain. The selection process of the study population was conducted in the only addiction clinic for the provision of methadone in both cities during the study period...”

- 2) Is it really impossible to add data about treatment compliance? This data would be extremely important and it would give a significant contribution to clinical practice.**

The reviewer would like to add comments on treatment compliance as a contribution to clinical practice in HCV cure. As mentioned in the Discussion section (limitations of the study), treatment compliance with DAAs was not analyzed in this study. However, please note that having results on Sustained Viral Response (SVR) would serve as surrogate of treatment compliance. As you can see in the Results section (page 9, 2nd paragraph), 90% of the patients treated with DAAs achieved SVR which suggests good therapeutic compliance.

- 3) In fact, as you highlighted in the paper, patients with HCV-HIV coinfection were twice as likely to receive DAA treatment, compared to those with HCV mono-infection, related to the risk of low compliance rate of this population - Do you have data about the reinfection rate after DAA treatment of this cohort of patients?**

The reviewer would like to add comments on HCV reinfection, a key point to eradicate HCV in this population. Unfortunately, reinfection rates were not analyzed in this study.

Reviewer #2: We read with great interest the study by Sanvisens et al. This study confirmed that the prevalence of HCV infection was high among

patients with SUDs that were treated with methadone or buprenorphine. Only 50% of patients with an anti-HCV positive test were treatment naïve. Lower rates of treatment among patients with HCV mono-infection than among patients with HCV-HIV co-infection.

- 1) However, the study lack of novelty since several other reports from different countries explored these aspects (PMID: 31178254, PMID: 30853642, PMID: 30174397). The authors should better underline the strenght and the novelty of the study, maybe skipping most of the descriptive section and focusing on the predictive factors associated to DAA treatment.

We agree with the reviewer. The study provides an excellent snapshot of the access to curative HCV treatment in a difficult to reach population and the novelty of the study is related to the predictive factors associated with HCV treatment. In addition, there are few longitudinal studies showing HCV treatment rates over time and this is the first in Spain reporting data on DAAs uptake while in an OTP. Studies mentioned by the reviewer (PMID 30853642 and 31178254) are clearly different in the design, objective and setting. The paper by Kranidioti et al (PMID 30174397) describes patients in an OTP having no access to HCV treatment with DAAs did not analyze predictive factors and treatment rates. However, we decided to include the three recent references suggested by the reviewer in the new version of the manuscript.

Following the comment from the reviewer we have made some modifications in the Discussion section to highlight the novelty and strengths of the study.

Specifically, we have added the following sentences:

“This study provides a snapshot of the access to curative HCV treatment in patients treated with methadone. Furthermore, it shows that after the introduction of DAAs in Spain...”

“... In contrast, our study population is anchored in an OTP with a large number of patients and real-world conditions which is relevant to generate evidence in a population difficult to treat and retain”

And we have removed the following from the Discussion section:

“...This study confirmed that the prevalence of HCV infection was high among patients with SUDs that were treated with methadone or buprenorphine....”

“...Indeed, in the present study, up to 90.4% of patients achieved SVR. A previous post-hoc multicenter clinical trial that compared HCV treatment outcomes in patients with and without opioid agonist therapy revealed that, among patients with treatment, a high percentage completed the HCV treatment and achieved SVR [21]. However, that same study showed that HCV treatment adherence was lower among patients on opioid agonist therapy (90%) compared to those not received therapy for substance use (94%). Nevertheless, among those that did not meet the adherence criteria, up to 63% achieved SVR [21],....”

2) Moreover, they should better explain which would be the reason of this low treatment rate in the different subgroups.

We are reporting an increasing proportion of HCV-positive patients going into HCV therapy since the introduction of DAAs (Figure 2). Nonetheless, we have included a new paragraph to discuss the reasons for having lower than expected treatment rates in the HCV-monoinfected patients with respect to the HCV/HIV-co-infected. This paragraph now reads as follow (Discussion section, page 10):

“... This finding might be related to differences in the continuum of care in the HCV mono-infected and the HIV co-infected. In Spain, HCV mono-infected patients receive regular care and treatment in hospital-based Hepatology units while HCV/HIV co-infected patients are managed in HIV/Aids units having integrated services, psychosocial support and flexible time-slots for visits....”