Author's response to reviews

Title: Personality disorders do not affect treatment outcomes for chronic HCV infection in Spanish prisoners. The Perseo Study.

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Author's response to reviews: see over
Dear Editor,

We thank the reviewers for their comments and suggestions, which we believe have helped to improve our manuscript MS: 6687210191599690, entitled: “Personality disorders do not affect the outcomes of chronic HCV infection treatment in Spanish prisoners. Perseo Study”.

Regarding your comment [“There is no doubt that this is an interesting paper on an important and difficult issue. The reviewers have made many major comments that need to be taken into account (particularly reviewer 1 and 2) including important issues regarding the validity of the PDQ-4], we would like to thank you for the opportunity to revise and resubmit our paper. We have commented on each point raised by the reviewers, and have made various changes in response to their recommendations. We believe that our responses to Reviewer 2’s comments will resolve any doubts you might have regarding i) the suitability of using the PDQ-4, and ii) its validity as a screening and diagnostic instrument for personality disorders.

We attach a revised version of the manuscript, which has been modified as per our responses to the reviewers comments as follows (changes introduced are highlighted in blue). We hope that you will find this revised manuscript suitable for publication in BMC Infectious Diseases.

We look forward to hearing your decision.

Andrés Marco
Joan A. Caylà
Reviewer #1:

1. I think there is a need for simplification in the different ways response to HCV treatment was measured: rapid viral response, early response, end of treatment response, SVR nested in ITT. What matters is whether or not patients receiving treatment were cured. I suggest to focus on SVR and discontinuation as outcomes.

We accept this recommendation and have simplified the analysis of efficacy (SVR) and discontinuation (see the Results section).

2. The authors should also better explain how ITT was computed.

This information is provided in the Methods section, subparagraph Statistical Analyses: “The results were analysed using intention-to treat (ITT) analysis (we analysed the results for all patients assigned to each treatment group, regardless of whether they completed the treatment and/or follow-up) and by observed treatment (OT) analysis (we analysed the results for patients assigned to each group and who completed the treatment and/or follow-up)”

3. In addition it would be interesting for the reader to clearly define the relationship between a specific PD and the outcomes (discontinuation and SVR) as the table is unclear: what are cluster A, B, C?

While we agree that such an analysis is relevant and may have value for some of the readers, we believe that exploring the relationship between specific PDs and the outcomes is beyond the scope of this article because of the limited number of patients with certain PD diagnoses (e.g. dependent, histrionic). Therefore, we prefer to maintain the original perspective of the analysis (based on the 3 specific subtypes or clusters of pathological personality) and the original format of Table 1.

Nonetheless, in response to comments from this and another reviewer, we have clarified this point in the revised version of the manuscript (Methods section, and Table 1).

4. Please better define all the different responses to HCV treatment (RVR, EVR, etc…) how ITT is computed and subscales of PD (cluster A, B, C).

i) Regarding the various responses to HCV treatment, this is no longer necessary because we have simplified the analysis of efficacy (SVR) and discontinuation as recommended by the reviewer (point 1).

ii) As for the definition of cluster A, B, and C, please refer to our answer to your comment above.

5. there too many tables and figures. In particular remove table 3 and figure 2 as this is not pertinent with the objective of the study.

We removed Table 3 and Figure 2, as suggested.

6. The authors should remove that the limits is the prison population. It is such a difficult task to conduct studies like this and it is normal that the results concern the prison population.

We have removed this point, as suggested.

7. Minor revisions: some names of variables in tables needs a legend.

We have modified the legend of Table 1 as follows:

OR: odds ratio; CI: confidence interval; IDU: injection drug use; BVL: baseline viral load; PD: personality disorder; AOR: adjusted odds ratio; Cluster A-PD: Paranoid, Schizoid and Schizotypal PDs; Cluster B-PD: Histrionic, Narcissistic, Borderline and Antisocial PDs; Cluster C-PD: Avoidant, Dependent and Obsessive-Compulsive PDs.
Reviewer #2:

1. **Additional detail should be included regarding the definition of “personality disorder”**.
   We have now incorporated a brief definition of personality disorder in the *Introduction* section.

2. **What is the sensitivity and specificity of the screening questionnaire that was used to ascertain personality disorder against a gold standard?**
   Perhaps we have not made it clear that the self-report screening questionnaire was not used for diagnostic purposes. To clarify this point, see *Methods*: ‘A two-step screening and diagnostic instrument for personality disorders’. A personality disorder diagnosis was made only when the interview-based Clinical Significance Scale confirmed that each positive-screening result for personality disorder actually met the general criteria for personality disorder diagnosis. That is, after performing screening using the self-report questionnaire, the interviewer uses the CSS to evaluate whether the interviewee responds positively to the items in questionnaire (A), for each positive PD. If confirmed, they are asked how long they have had these characteristics (B), their dependence or independence in relation to other mental disorders (e.g., depression, anxiety disorder, SUD) or medical conditions (C), difficulties or impairment they may have within the family, social circle, and/or work environment (D) and, finally, concern or stress caused by these characteristics (E). To be considered as having clinically significant PD, the number of criteria met after the interview must continue to be higher than or equal to the threshold or cut-off score, as well as meeting conditions A, B, C, and D or E.

Moreover, there is no single, widely-accepted gold standard for estimating the validity of screening or diagnostic instruments for personality disorders. All assessment approaches have strengths and weaknesses (e.g. self-report measures, structured clinical interviews, unstructured clinical interviews, information obtained from knowledgeable observers). In fact, it is becoming widely accepted that multi-method assessment must play a central role in the diagnosis of personality disorder.

Regardless, we have not found previous studies that evaluate the sensitivity and specificity of the complete PDQ-4+ (i.e. not just the self-reported screening questionnaire) against other instruments and/or methods.

3. **What is the clinical significance of a positive result on this instrument?**
   We are not entirely clear about what the reviewer means by “this instrument” (i.e., only the self-reported screening questionnaire or the complete PDQ-4+). Although a threshold may be reached on the self-reported screening questionnaire for a specific personality disorder diagnosis, a clinician would not judge the pathology as being clinically significant. The result is only considered clinically significant when the interview-based Clinical Significance Scale confirms a positive-screening result for a personality disorder. Using the Clinical Significance Scale, the interviewer checks with the patient that: a) there was no mistake in endorsing the items; b) the traits have been present since about age 18, or for the past several years; c) the traits are not primarily due to axis I conditions such as anxiety disorder, mood disorder, substance/alcohol abuse or physical condition, and that either d) the traits have caused significant difficulty for the patient at home, at work (or school) or in their relationships, or e) the patient feels bad about himself/herself because of the traits. Clinical significance thus implies that the number of criteria met after the interview continues to be higher than or equal to the threshold score, and that conditions A, B, C, and D or E are met.

4. **Has the instrument been validated in an incarcerated population?**
   Yes. In response to this question, we have now included this information in the revised version of the manuscript (see “A two-step screening and diagnostic instrument for personality disorders” in the *Methods* section).
5. Who administered the test, and what was their level of expertise?
The self-report screening questionnaire was self-administered by the patients themselves during a medical consultation (see the Procedure sub-section of the manuscript) and the interview-based Clinical Significance Scale was administered by a clinician – usually the physician in charge of the inmate’s medical treatment and, therefore, with long-term knowledge of the patient – during a subsequent medical consultation. All clinicians received previous training in administering the PDQ-4+ from a psychiatrist and a clinical psychologist (see the Discussion section of the manuscript). In any case –and quoting the PDQ-4 instructions–, note that “PDQ-4 supports the assessment of clinical significance by either a clinician or paraprofessional rater”.

In response to this question, we have added more information on this point to the Methods section (Procedure subsection).

6. Given the high prevalence of PD in the study sample as defined by the instrument, might there be issues with positive predictive value?
In the absence of a gold-standard test (see responses to comments 2 and 7), this possibility cannot be definitively ruled out at this time, although it seems unlikely since the prevalence observed in our study (72.5%) is reasonable when one considers the following: i) it is comparable to rates reported for other prison populations (mean = 65%; see the systematic review cited in the Discussion section), and ii) the fact that nearly 80% of the patients in this study had a history of IDU (personality disorders are commonly overrepresented among individuals with current or lifetime substance-use disorders).

7. Are there more rigorous estimates of the prevalence of diagnosed PD in Spanish prisoners which this estimate could be compared against?
Unfortunately, there are no other rigorous estimates of the prevalence of personality disorders in Spanish prisoners, as far as we are aware. Somewhat similar studies used only a self-reported screening questionnaire (the International Personality Disorders Examination [IPDE] self-report screener in Vicens et al., 2011), a self-reported inventory (the Millon Clinical Multiaxial Inventory-II [MCMI-II] in Fernández-Montalvo & Echeburúa; 2008), or an unstructured clinical interview (Arnau-Peiró et al., 2012). In contrast, we used the complete PDQ-4+ instrument (i.e. the PDQ-4+ self-reported screening questionnaire, and the structured, interview-based Clinical Significance Scale).

In response to this question, we have added a comment to the Discussion section to contextualise our prevalence data in relation to those from other studies.

A brief search returned the following article, which demonstrates the poor positive predictive value of the PDQ-4 against another instrument, the SCID-II – it appears that the PDQ-4 returns prevalence estimates for several personality disorders orders of magnitude higher than the SCID-II. Given that prisoners will necessarily satisfy some diagnostic criteria for some personality disorders (criminal justice involvement) and are very likely to satisfy others (risk taking behaviour), the validity of the prevalence estimate presented here is questionable, and it seems possible that substantial misclassification may have occurred. Possibly this could be addressed by repeating the analysis using a higher cut-off value on the instrument to indicate PD?

We agree that screening instruments tend to over-diagnose personality disorders. For this reason, we specifically use the complete PDQ-4+ (see Method), not just the self-reported screening questionnaire. Note that, in contrast, de Rues et al. (2013) used only the screening self-report and not the complete PDQ-4+. The
The complete instrument also includes the valuable interview-based Clinical Significance Scale to assess whether each positive-screening result for PD actually met the general criteria for PD diagnosis. The latter is particularly important because the self-reported screening questionnaire is not a substitute for the complete PDQ-4+.

We also agree that prisoners will likely satisfy some diagnostic criteria for some personality disorders. However, this is a limitation of the classification/diagnostic systems in use (e.g., DSM, ICD) and not of the instruments themselves. In any case, since we used the complete PDQ-4+ (and therefore a diagnosis of personality disorder was made only after the interview-based Clinical Significance Scale), repeating the analysis using a higher self-report cut-off value to indicate probable PD would not change the results.

8. Given the high prevalence of PD and the small sample, was the study adequately powered to detect a clinically significant difference in treatment completion? Only 49 participants without PD were included as the comparator. Are there previous estimates of the impact of PD on SVR which might be used as indicators of the expected difference in outcome?
   i) The study was conducted in all prisoners (not a small sample) with or without PD who were treated with Peg-IFN α2a plus ribavirin in 25 prisons in Spain between 01.01.2011 and 31.12.2011. The PDQ-4+ was valid in 178 prisoners (75.4%), 129 of who had PD and 49 who did not. This distribution is consistent (see responses to comments 2 and 7) and the size of the study is sufficiently large to detect statistically significance effects.
   ii) As far as we are aware, this study is the first to evaluate whether PD can influence the effectiveness and discontinuation of chronic HCV infection treatment.

9. If PD was only assessed in 178 participants, then in my opinion all analyses should be restricted to this sample. In the results section, discontinuation is calculated using the initial sample of 255 as the denominator, but then reasons for discontinuation are referred to as not differing between those with and without PD - presumably the 77 participants among whom PD could not be assessed were not included in this analysis? For simplicity, I would recommend excluding them from all analyses and mentioning them only in the Methods section.

In the updated version of the manuscript, we have clarified the rate of treatment discontinuation according to whether or not PDQ-4+ was measurable, as suggested by the reviewer. We have analyzed all patients and have specifically compared the effectiveness and rate of treatment discontinuation among cases with PD and those without.

10. The result presented is not one of non-inferiority, as the authors imply in their discussion- in fact, it indicates that participants without personality disorder were significantly more likely to discontinue treatment than those with PD. This is counter-intuitive, and in my opinion requires explanation. For example, it may be the case that participants with PD have a greater frequency or intensity of contact with health services, which improves the management of adverse events during HCV treatment. It may also be the case that some participants with PD were already on psychiatric medication prior to HCV treatment initiation, which may have a protective effect with regard to psychiatric adverse events. In the absence of such an explanation, though, the result seems unlikely to reflect a genuine causal relationship, and this should be explored. In addition to my concerns about the validity of the PDQ-4 instrument in this population, I would suggest assessing the affect of discontinuation due to early release or transfer on the results. If participants with personality disorder were less likely to be released early or transferred, either for reasons related to the PD or due to common causes (e.g. age and sex, which were not included in the multivariate model as potential confounders), this would cause biased attrition which may explain the unexpected result. Given that early release / transfer accounted for 35% of discontinuations, the impact of
this may be substantial. If participants who discontinued due to early release or transfer are excluded from
the analysis entirely, what is the result? Does the apparent association between PD and treatment
completion persist? If the analysis is further restricted to participants with a measured SVR, what then?

In line with the reviewer’s comment, we have further highlighted the fact that the rate of treatment
discontinuation was lower among patients with PD. As noted in the manuscript and in Figure 2, there were
no differences between cases with PD and those without in the rate of discontinuation due to adverse
effects or penitentiary reasons (release and/or transfer between prisons).
As the reviewer suggests, we have reviewed the number of participants with PD who were already on
psychiatric medication before starting HCV treatment, and found it to be significantly higher in cases with
PD. This may have a protective effect on adverse psychiatric events, possibly resulting in a lower rate of
treatment discontinuation (see Results section).

Minor Essential Revisions

11. **Introduction:** It would be good to clearly state whether PD is a contraindication for HCV treatment in
Spain or the Spanish prison system, or whether the exclusion of patients with PD from treatment is the
result of case-by-case clinical assessment.

We have added the following comment to the Introduction section. “Treatment for HCV infection is not
contraindicated for Spanish prisoners with PD”.

12. **Results:** The variety of outcome measures used is confusing, and requires further justification and
explanation. Why was treatment outcome described using three different indicators (RVR, Early VR, End
VR)?

We have simplified the analysis of efficacy (SVR) and discontinuation (see response to Point 1, Reviewer 1).
Reviewer #3:

The typographical errors listed by the reviewer have been corrected.