Author's response to reviews

Title: Sex-specific disease outcomes of HIV-positive and HIV-negative drug users admitted to an opioid substitution therapy program in Spain: a cohort study.

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

We are submitting the revised version of the manuscript entitled “Sex-specific disease outcomes of HIV-positive and HIV-negative drug users admitted to an opioid substitution therapy program in Spain: a cohort study.” to be considered for publication in your journal.

We appreciate the opportunity to revise and resubmit, and we believe that all the reviewers and editor comments have been addressed. We also believe that our responses will strengthen the manuscript.

Looking forward to hearing from you.
Sincerely,

Roberto Muga, MD, MPH
Referee 1
Reviewer:
Sarah Larney

Reviewer's report:
This is an observational cohort study of mortality among people entering an opioid treatment program in Spain. HIV infection predicted mortality among men and women. Although mortality rates among HIV-infected men have decreased, mortality rates among HIV-infected women have been increasing.

Introduction:
1) Second sentence: “Injection drug users are more likely to...” More likely than who? Rather than make a comparison, might be best just to note that they have a high prevalence of infections etc.
2) The first paragraph is a little confusing. The first sentence talks about what heroin addiction is, the second about risks associated with injecting drug use, and the third about the prevalence of heroin ‘abuse’. These sentences could be harmonised a little so that we see a clearer flow of ideas.

According to the two comments raised by the reviewer, we have changed the first paragraph of introduction section as follows (Introduction section, first paragraph):

“It has been estimated that 1.35 million people are heroin users in European countries [1]. Heroin dependence is a chronic disease characterized by compulsive drug-taking behavior despite serious negative consequences and, specifically, injection drug users (IDUs) have high prevalence of severe co-morbidities including blood-borne infectious diseases, drug overdose, and psychiatric disorders [2–4]....”

3) Second paragraph, second sentence: I’m not sure that reduced heroin use facilitates the development of harm reduction interventions. Do the authors mean that reduced heroin use facilitates engagement with harm reduction programs? I’m not entirely sure of what the authors are saying, or whether the
cited references support these statements. I have some more specific points on a similar note later in this review.

In order to avoid any misinterpretation, we have reworded the sentence as follows (Introduction section, 2nd paragraph):
“…A reduction in heroin use further increases adherence to substitution therapies and facilitates the implementation of harm-reduction interventions aimed to improve quality of life and health…”

4) ‘MTPs have been used for decades’ – please be more precise (e.g. since the 19xxs)
We thank the reviewer for pointing out this imprecision. Accordingly, we have added the following sentence in the introduction section (Introduction section, 2nd paragraph):

“…MTPs have been used since the mid-1960 in the United States (U.S.)[10],…”

5) The authors cite a Cochrane Review that found a 25% reduction in mortality associated with methadone maintenance as compared with no treatment. I cannot see where in the cited reference the authors found this statistic. In the Cochrane Review, Mattick et al. reported a RR of 0.48 (95% CI 0.1-2.39) i.e. a non-significant result. This, however, is likely because randomised controlled trials (the only type of studies included in that Cochrane Review) are not usually statistically powered to detect differences in mortality between groups. Larger observational studies and meta-analyses of these have provided very good evidence of reduced mortality while in methadone compared to time out of methadone e.g. Degenhardt L., et al. 2011. Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. Addiction, 106, 32-51. The authors should update this section of the manuscript and citation.

According to the reviewer comments we have changed the suggested reference and updated the text. The new sentence now reads as follows (Introduction section, 2nd paragraph):
“...Most importantly, treatment with methadone has been shown to reduce the risk of death as compared to no treatment [13]...”

6) In the same paragraph, the authors cite several studies that they say support the statement that methadone reduces risk of blood borne viral infections. Again, there are problems with the references and even the statement itself in relation to HBV/HCV. In relation to methadone and HIV prevention, rather than citing a qualitative review, the authors would be better to cite a study that actually found an association between methadone and reduced HIV risk e.g. Macarthur G. J., et al. 2012. Opiate substitution treatment and HIV transmission in people who inject drugs: Systematic review and meta-analysis. BMJ, 345, e5945; Kimber, J., et al 2010. Survival and cessation in injecting drug users: Prospective observational study of outcomes and effect of opiate substitution treatment. BMJ, 341, c3172. In relation to HBV/HCV, to my knowledge, the cited reference – nearly ten years old - does not find that methadone reduces the risk of HBV/HCV infection. It can, however, be argued that methadone in combination with other interventions, such as needle and syringe programs, can reduce risk of HCV – see for example, Holly Hagan’s work Hagan, H., et al. 2011. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. Journal of Infectious Diseases, 20, 474-483.

We would like to thank the reviewer for this very thoughtful comment. We have revised the sentence accordingly and we have also updated the references. In the updated version of the manuscript, the sentence now reads (Introduction section, last sentence of 2nd paragraph):

“...Treatment with methadone also reduces the risk of blood-borne infections, such as human immunodeficiency virus (HIV); methadone treatment in combination with needle exchange programs and other harm reduction strategies has been shown to reduce the risk of hepatitis C virus (HCV) infection [14–16]...”

7) Paragraph 3 of introduction: can the authors please clarify what is meant by ‘when OST was generalized’?
To better clarify the concept we have changed this phrase as follows (Introduction section, 3rd paragraph):

“…Approximately 90,000 patients receive methadone treatment in Spain, and this figure has remained constant since the early 1990’s, when OST was focused to reduce the impact of HIV/AIDS and drug overdose [17]…”

8) Citation 7 – this citation does not itself find that there was a reduction in life expectancy for the general population. Please cite the original source.

We have changed the reference using the original source, which is reference 18 in the updated version of the manuscript.

9) The description of the four time periods analysed may be better placed in the methods.

We thank the reviewer for pointing this out, and the four time periods are now described in the methods section.

10) Please spell out the acronym ‘QD’ the first time it is used – I have no idea what it means.

QD (Quaque Die) means once-daily dose. To avoid any misunderstanding, we have changed “QD” in the manuscript body and now it reads “once-daily dosing” in the material and methods section.

Methods:

11) I’m a little confused about which patients are included in the study – are the community pharmacies part of the MTP that the patient data are from?

This study includes all patients admitted in a MTP program from January 1992 to December 2010. The MTP program is managed from an Addiction primary care center, and there is where patients were included and where methadone treatment is indicated.

The mobile unit and the community pharmacies mentioned in material and methods section are only dispensing units.
12) Although the authors note that the study complied with ethical standards for medical research, I would like them to confirm that the study was reviewed by an ethics committee or institutional review board.

**This study was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol. We have included this information in the Methods section, 7th paragraph.**

13) The authors state “Only the first admission for patients with multiple admissions to the MTP was analyzed”. Does this mean that only the period when the person was in treatment for the first time was included in follow-up? Because the median follow-up time would suggest that person-years were counted from time of first entry to treatment to the end of the follow-up period or death, whichever was first. As it stands, all that the first admission to MTP really does is mark the participant’s entry to cohort. It’s not really analysing it at all – so some rewording seems necessary.

In this study, person-years of follow-up accounted from the time of first entry to MTP (patient’s entry to the cohort) to December 31st, 2010 or death (end of follow-up).

In order to avoid any confusion, we have reworded the material and methods section (Statistical Analysis section, 1st paragraph):

“… Patients’ entry to the cohort was defined by the first admission to MTP; all patients were followed until December 31st 2010 or death…”

14) This raises an important question - why is movement in and out of methadone not included in the analysis as a time-dependent covariate, particularly given how important methadone is in moderating mortality in this population, and the often cyclical nature of treatment? This is a major limitation of the study.

We agree with the reviewer on the importance of the movement in methadone treatment. Unfortunately we did not have this information, as noted in the discussion section, 8th paragraph:

“…Third, as mentioned before, this study did not analyze methadone dose changes and treatment interruptions over time; in this regard methadone dose, interruptions, and compliance have been associated with disease outcomes. …”
15) Cox proportional hazards model: I have more to say about this in the results, but for now, can the authors please note if they tested the proportional hazards assumption and the results of this test?

In order to clarify the statistical methodology used around the Cox regression model, we have added more information that reads as follows (Methods section, 2nd paragraph of Statistical Analysis):

“…Cox regression models were used to analyze the predictors of death. Previous to the implementation of statistical models we checked for the proportional hazards assumption of all variables. The covariates used for the multivariate analysis were those that were found to be statistically significant in univariate analysis. Stepwise forward selection was used to identify predictors establishing $\alpha=0.05$ and $\alpha=0.1$ as the inclusion and exclusion criteria, respectively. …”

16) The authors need to clarify the period of time over which person-years accrued – I assume it is from first entry to treatment until death or end of follow-up (please provide date). Poisson confidence intervals should be calculated for the mortality rates.

Please note that according to previous comments, we have specified this information in the Methods section. See also response #20.

On the other hand, the confidence intervals are calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter. As mentioned before, we have also added the CI for overall mortality.

17) Were HIV/HBV/HCV diagnoses updated throughout the analysis, or did the analysis only include infectious diseases at the time of first entry to treatment?

Information about HIV/HBV and HCV infections were only available at admission. Please see also response #21.

Results:

18) Table 1: For variables with missing data, it is not possible to tell the denominator for men and women separately, as the authors have only provided the
denominator for the total sample. Please revise the table so that the denominators for men and women are clearer.

We believe that including denominators for men and women separately would make the table more difficult to read.

As can be seen in the table provided, there are no differences between men and women regarding the availability of variables.

<table>
<thead>
<tr>
<th></th>
<th>Male (N=1390) n available (%)</th>
<th>Female (N=298) n available (%)</th>
<th>P_value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug use</td>
<td>1291 (92.9)</td>
<td>271 (91.0)</td>
<td>0.248</td>
</tr>
<tr>
<td>Unemployed</td>
<td>1289 (92.7)</td>
<td>271 (91.0)</td>
<td>0.289</td>
</tr>
<tr>
<td>Primary school attainment</td>
<td>1281 (92.1)</td>
<td>271 (91.0)</td>
<td>0.483</td>
</tr>
<tr>
<td>Prior incarceration</td>
<td>1226 (88.2)</td>
<td>254 (85.2)</td>
<td>0.157</td>
</tr>
<tr>
<td>HIV-infection</td>
<td>1109 (79.8)</td>
<td>234 (78.5)</td>
<td>0.624</td>
</tr>
<tr>
<td>HCV-infection</td>
<td>605 (43.5)</td>
<td>122 (40.9)</td>
<td>0.413</td>
</tr>
<tr>
<td>HBV-infection (HBcAb+)</td>
<td>593 (42.7)</td>
<td>115 (38.6)</td>
<td>0.196</td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>1293 (93.0)</td>
<td>274 (91.9)</td>
<td>0.513</td>
</tr>
</tbody>
</table>

19) In reporting mortality rates, please use the format x.x per 100 py.

We have changed the reporting of mortality rates as the reviewer suggests,

20) The first mortality rate under ‘follow-up and outcomes’ is reported with an IQR rather than CI – please provide the CI.

We thank the reviewer for picking this error. The current version of the manuscript now provides the CI. Please see Results section, 4th paragraph that now reads:

“…The overall mortality rate was 2.9 per 100 p-y (95% CI: 2.6-3.2 per 100 p-y),...”

21) When discussing predictors of death, it is important to note that it is period of FIRST admission to treatment that is being examined. Similarly, HIV status AT BASELINE was an independent predictor of death (unless HIV status was updated if a participant became infected?).
We thank the reviewer for pointing out this potential inaccuracy. HIV infection and all the other predictors of death were at baseline, that is, at admission to treatment. In order to avoid any misunderstanding, we have reworded the following paragraphs (5th and 6th) from the results section and now reads:

“…In the univariate analyses, age at admission, antecedent of IDU, HCV, HIV and HBV infections at admission, prior incarceration, and period of admission to MTP were associated with mortality among men. In the multivariate analysis, only HIV infection at admission was an independent predictor of death (Table 3).

Among women, age at admission, antecedent of IDU, HBV and HIV infection at admission, and prior incarceration were associated with mortality in the univariate analyses. In multivariate analysis, only HIV infection at admission and prior incarceration were predictors of death (Table 3)…”

22) Table 3: The multivariable columns do not appear to include all variables that were in the multivariable analysis (because in the men’s analysis, the univariable and multivariable HRs for HIV infection are different, despite the multivariable analysis appearing to only include one variable).

As mentioned, in the response to comment # 15, stepwise forward selection was used to identify predictors establishing $\alpha=0.05$ and $\alpha=0.1$ as the inclusion and exclusion criteria, respectively.

Therefore, we only show results for the covariates that were included in the final adjusted model.

23) In the methods, please report the modelling strategy e.g. how variables were selected to be included in the multivariable model (what p value was used to determine this? Hosmer and Lemeshow recommend <.25), and how were variables entered into the model? Hosmer and Lemeshow recommend putting all univariate p <.25 in the model, and that’s the final model – I recommend this method.

Please see response #15
24) Mortality trends – the authors state that mortality rates decrease significantly over time – what test was used to support this statement? What are the test statistics?

In the present study, the test used to support this statement was a relative risk of death between the first period vs any other period. We have reworded this section to better clarify our approach, and now reads (Results section, 7th paragraph):

“…Overall mortality rate decreased over time: 7.4 per 100 p-y (95% CI: 6.3-8.8 per 100 p-y) for 1992-1996, 2.7 per 100 p-y (95% CI: 2.2-3.3 per 100 p-y) for 1997-2001, 2.4 per 100 p-y (95% CI: 2.0-2.9 per 100 p-y) for 2002-2006, and 1.9 per 100 p-y (95% CI: 1.6-2.4 per 100 p-y) for period, 2007-2010. A significantly significant reduction (p<0.005) for all pairwise relative risk of death was observed using the first period as the reference category…”

25) The presentation of mortality trends is somewhat confusing. Rates in text refer to the total sample, and then by sex, but rates in the figure show rates by sex and HIV status at baseline.

We believe that providing mortality information for the whole study population and then stratified by sex and by HIV status is of interest for the reader. We have rewritten the results section (both in the abstract and in the manuscript body) to avoid any confusion.

26) I’m not sure that the retrospective analysis of deaths in HIV-infected women adds much unless you also look at recently deceased HIV-infected men for comparison. I will go into this in further detail below.

According to the reviewer’s concern, we have deleted the retrospective analysis of the 33 HIV-infected women that died in the period 2002-2010. We have also rewritten the discussion section accordingly. Please see the new discussion section.
Discussion:
The discussion is somewhat unfocused and a bit superficial in its examination of the results. It needs a thorough revision.

27) Reference 24 does not, as far as I can tell, have anything at all to say about methadone being the preferred drug for treatment heroin addiction in Western countries. That’s not really a relevant statement, anyway – delete and focus the discussion on the findings and integrating them into the literature.

According to the reviewer comment, we have deleted the first paragraph of discussion section.

28) Paragraph 2, sentence 2: “that also showed a significant impact of HIV/AIDS on MTPs” – has this study really shown an impact of HIV on methadone treatment programs? Do you mean an impact on patients? Or impact on mortality of this group? I’m not sure what the authors are trying to say here.

In order to avoid any confusion, this sentence has been deleted from the updated version of the manuscript.

29) Third paragraph, second sentence – not really relevant; the first sentence of this paragraph is about characteristics of HIV-infected women who had died, so the rest of the paragraph should be about the same thing.

The discussion section has been extensively rewritten and this sentence has been deleted.

30) The authors recommend directly observed HAART. However, this makes an assumption that it is poor HAART adherence that is leading to deaths. On the basis of the evidence presented in this study, we don’t know that this is the case. Not all deaths of HIV-infected women were AIDS-related, for one thing. There is no comparison of HAART adherence in deceased men – if we knew that deceased men had better adherence, then there might be some indication that measures to improve adherence among women specifically are needed. Assuming that interventions are indeed needed to improve clinical care of HIV-infected women in this group, why directly observed therapy? Why not looking at why the women are having problems with adherence, and helping them address these?

As reviewers have expressed concern, we have deleted the retrospective analysis from the results section and it is not mentioned in the discussion.
The inference around HAART adherence and management of HIV-infected women on MTP has also been deleted.

31) The results from citation 38 have been misinterpreted. The authors have mistaken the standardised mortality ratio, which calculates excess mortality in one group compared to another, for the standardised mortality rate. Non-natural causes of death in the study cited are higher among men than women. The ratio of deaths in women in opioid treatment to the general female population is higher than the ratio of deaths in men in opioid treatment to the general male population. This is not the same as mortality RATES are higher in women than in men.

The body of the discussion has changed, and according to the reviewer comment, that sentence now reads (Discussion section, 4th paragraph):

“…However, a recent study on patients in a MTP demonstrated that the excess mortality due to non-natural causes is higher in women when the standardized mortality ratio is considered [30]…”

32) In discussing MTP admissions over time (which is not all that relevant and could probably be deleted anyway), the authors should note that they are talking about FIRST TIME admissions to treatment, not overall admissions. These are very different statistics.

In the present study, we analyze first time admissions to a specific MTP over time. Assuming that access to MTP does not change, we have seen a reduction in the number of patient over time.

This is, of course a collateral finding of our study, and it is mentioned as such in the results and in the discussion section.

33) Line 304 onwards: “highlighting the impact of OST…” – no. The decision to exclude data on OST retention, drop out and re-entry means that the authors cannot say anything meaningful about the impact of OST on mortality in this cohort. At best, the study describes mortality in a cohort of opioid dependent people who have sought treatment at some point. It cannot provide information on the impact of OST on mortality unless the authors include data on OST retention in the analysis.
According to the reviewer comment we have delete this phrase.

Level of interest:
An article of importance in its field

Quality of written English:
Needs some language corrections before being published

Statistical review:
Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests
Referee 2
Reviewer's report
Title:
Gender disparities in the survival of HIV-positive drug users admitted to an opioid substitution therapy program in Spain: a cohort study.
Version:
1
Date:
16 April 2014
Reviewer:
Catherine Todd
Reviewer's report:
Major Compulsory Revisions
Abstract/Summary:
• The purpose statement does not mention anything about gender difference but the title of the manuscript indicates that this is the focus of the paper. Please revise one or the other.

The purpose statement in abstract now reads as follows:
“...We aimed to analyze sex differences in mortality rates and predictors of death among those admitted to a methadone treatment program (MTP)....”
• Were death rates significantly different between men and women? Wouldn’t it make more sense to state that directly and then comment on whether key predictors were similar or different by gender? The way the Results are currently presented does not support the manuscript’s title.

As seen in table 2, there were no differences in the overall mortality rate between men and women (p=0.187).

Predictors of death only differed in that prior incarceration was associated with mortality in women but not in men.

Following the comments raised by the two reviewers, we have extensively rewritten the abstract, results and discussion section. In addition, we have also changed the manuscript title and now reads:
Sex-specific disease outcomes of HIV-positive and HIV-negative drug users admitted to an opioid substitution therapy program in Spain: a cohort study.
• The conclusion statement does not indicate why mortality among women increased. Please revise the Results section to provide this evidence and then revise the Conclusions statement.

In the new version of the manuscript, trying to address many of the comments raised by both reviewers, both the results and the conclusion sections have been reworded. In addition, the stress that in the initial version was made around the increasing deaths among women has been toned down, especially in the discussion section.

Introduction:
• The first sentence of the last paragraph states that the paper aims to assess differences in survival between injectors and non-injectors. If this is the outcome of interest, why is it not mentioned in the title or abstract? If not, this sentence should be revised to reflect an analysis constrained to IDUs with the outcome of interest being differences in mortality between men and women.

The main objective of the paper was not to find differences in mortality between those who had injected heroin and does who had not. We have changed the first sentence of the last paragraph of the introduction section, and now it reads:
“…The aim of this study was to analyze the survival of heroin users and predictors of death in a cohort of patients admitted to a MTP….”

• The description of the calendar periods based on temporal events should be placed in a Measures section of the Methods. The key events that determine the divisions can be mentioned in a sentence or two in the Introduction. This paragraph should instead end with the anticipated value or use of the results for OST/SIF programs in Spain.

The description of the calendar periods now appears in the Methods section. In addition, we have added a sentence at the end of the introduction so as to address the last part of the reviewer comment (Introduction section, last sentence):
“…In doing so, our results will inform how MTP is implemented in our area.”

Methods:
• While the statement that the study is compliant with the Declaration of Helsinki is appreciated, there needs to be a statement confirming review and approval of this study prior to data collection by an ethical review board. Even though data were collected by chart review, ethical board review is still required, even if they determine the study to exempt from review.

This study was approved by the Ethics Committee of the Hospital Universitari Germans Trias i Pujol. In the revised version of the manuscript, we have included this information in the Methods section, 7th paragraph

Results:
• The first three paragraphs could be made more concise with this data incorporated into Table 1 and with columns reporting, for each characteristic, the overall statistic, then specific statistics for men and for women.

According to the reviewer comment we have revised the length of the first three paragraphs. Please note that in the manuscript body the reviewer can find the results for the overall study population, while in Table 1 the results are stratified by sex.

• It is only first clear in this section that both injecting and non-injecting users are included in the analysis. The Methods section needs to include a statement to this effect and a rationale for including both groups, given their very different mortality risks.

Please note that we did not exclude non-injection drug users from the study population. The material and methods section states that the covariates around drug use characteristics are “age at first consumption, duration and route of administration”.

Route of admission is included in the Cox regression analysis, and while injection drug use is associated with overall mortality for men and women in the univariate analysis, it is no longer significant in the final adjusted model.

• History of overdose is not reported in the Results yet seems a probable predictor of mortality. Please add this descriptor or provide explanation in the Methods why this is not possible (may not be available in the MTP charts).
As it is clearly stated in the discussion section, the number of available clinical and epidemiological variables is limited. Unfortunately, information about history of overdose is not available.

- Line 169: What is an “antecedent of imprisonment”? Does this mean previously incarcerated or were referred to the program directly from prison? Please use a different term for this characteristic, such as prior incarceration.

According to the reviewer suggestion, we have changed this term with “prior incarceration” throughout the document

- Lines 256-264: The paragraph states that female IDUs are at greater risk for not accessing harm reduction, yet this study includes only those patients of MTPs. There was no data presented regarding OST adherence in the results but we must assume that these patients were adherent to have the follow-up data. The authors need to comment on the potential bias in this population. Further, stigma against female IDU is not a new concept – has something happened more acutely to result in the recent upswing in mortality among HIV-infected female IDUs? Is there anything that would contribute to them not getting ART on a regular basis? Possibly incarceration? How many are sex workers and would this increase their risk of arrest and inability to adhere to ART?

The reviewer raises a very important comment. Unfortunately, we did not have many of the information available that the reviewer suggests us to include. The current version of the results and the discussion section has been rewritten, and the emphasis on the increasing mortality among HIV-infected women has been toned down.

Discussion:
- The statement “In addition, a percentage of the mortality is due to gender-specific clinical conditions, such as cervical cancer” has no data to support it from the Results section. Further, this paragraph leads to more questions than it answers. There needs to be corresponding data in the Results about the CD4 count at ART initiation and presence of HIV RNA for male patients to provide an adequate comparison. Also, there is no mention of methadone
adherence in HIV deaths for either male or female patients in the Results section. This is an important issue as combined OST-ART therapy models have been successfully tested and improve adherence of both medications as well as adjust methadone doses to remain effective in the presence of ART.

As it has been previously mentioned, the results section and the discussion has been extensively rewritten. We hope that in doing so we have answered many of the comments from both reviewers. Please see also response #30 from reviewer 1.

• The second-to-last paragraph does not mention the focus on gender-based differences and there is also no mention of improving mental health service access within MTPs as a recommendation. The manuscript would benefit from closer attention to the analysis purpose in the communicated messages.

The discussion section has been rewritten so as to address this comment.

• It was surprising that injecting drug use was not independently associated with mortality and is worthy of comment in the Discussion.

Injection drug use was not independently associated with mortality, probably because part of the observed association in the univariate analysis was driven by HIV infection. Accordingly, the new version of the discussion section now reads (Discussion section, 5th paragraph):

“…As it has already been mentioned, HIV/AIDS was a strong predictor of death, irrespective of gender. The results are consistent with others that have also showed a significant impact of HIV/AIDS on the survival of patients in a MTPs [7, 31–33]. Furthermore, HIV infection is patients on OST is a surrogate of injection drug use; in fact, non-IDUs have a fivefold lower risk of HIV infection than IDUs, as shown in previous studies [34,35] …”

• The limitation of not analyzing methadone dose change or interruption over time should be mentioned earlier in the Discussion as this is likely contributing to some of the mortality ascribed to other causes, particularly for HIV-infected patients.

The limitation of not analyzing methadone dose changes or interruptions appears earlier in the discussion section. The new version of the paragraph reads as follows (Discussion section, 3rd paragraph):
“…Regarding other factors that may influence survival of patients admitted to an OST, we cannot exclude the role that methadone dosage changes and treatment interruptions may have on mortality, as this information that was not available…."

Minor Essential Revisions:

Abstract/Summary:
- The title refers to heroin “users” while the abstract mentions “abusers”. It would be best to use the same term consistently and user is more neutral.
- The title has been changed and now reads: “Sex-specific disease outcomes of HIV-positive and HIV-negative drug users admitted to an opioid substitution therapy program in Spain: a cohort study.”.

Following the reviewer comments, the term “users” appears now throughout the updated version of the manuscript.
- The meaning of calendar periods is not clear – please define these in the Methods.

The calendar periods are now defined in the methods section. Please see response #9 to reviewer 1
- The nomenclature for mortality rates is not standard: it should be the number of deaths/100 p-y, not x100 p-y.

Please see response #19 to reviewer 1.

Introduction:
- Line 67: Please spell out U.S. the first time it is used.

Done.

Methods:
- Line 109: Should this be “>18 years old”? Also, were these entry criteria for MTPs overall or inclusion criteria for this analysis? Please specify.

MTP admission criteria were as follows: patients had to be >18 years old, and had to have an opioid dependence.
- Lines 147 and 148: The terms quantitative and qualitative variables are not standard. Do the authors mean continuous and dichotomous or categorical variables? Please revise.

We have revised the sentence according to the reviewer comment and now reads (Methods section, 1st paragraph of Statistical Analysis):
“...Descriptive statistics were expressed as the median (interquartile range [IQR]) for continuous variables and as absolute frequencies and percentages for categorical variables...”

Results:
• Lines 199, 203-204: The multivariate analysis results are stated in Table 3 and do not need to be repeated in the text.

As suggested by the reviewer, we have deleted this information in the updated version of the manuscript.
• The paragraph on mortality trends should indicate whether the rates stated as declining over time describe the population overall or are just for male patients.

The updated version of the manuscript clearly states that mortality rates decrease for the overall population. Please see response #24 for reviewer 1.
• Line 224: IDU is an injecting drug user. Please do not use it as a verb.

We have reworded the sentence accordingly.
• Same comment as in the Abstract for nomenclature for person-years.

We do not think that person-years are used as a verb in the abstract section, and only appear as a unit of mortality rates.

Discussion:
• The first paragraph is already communicated in the Introduction; please remove it from the Discussion.

We have removed the paragraph of the discussion according to this reviewer’s opinion and to question #27 from reviewer 1

Discretionary Revisions
Some members of the harm reduction community oppose the term “addiction” and instead prefer “drug dependence” or “problem drug use”. The authors may want to consider revising their terminology.

The term “Addiction” has been changed for dependence throughout the document
• The information from citation 38 does not appear to support the data in this study – please consider whether it should be included or a better way of phrasing whether the results of this analysis wholly mirror those of other studies or if other studies have mixed results to date.

Please see response #31 from reviewer 1
Level of interest:
An article whose findings are important to those with closely related research interests

Quality of written English:
Acceptable

Statistical review:
Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests