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  
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**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:**

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.

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.

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.

‘MTPs have been used for decades’ – please be more precise (e.g. since the 19xxs)

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.

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.

Paragraph 3 of introduction: can the authors please clarify what is meant by ‘when OST was generalized’?

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.

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

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

Methods:

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?

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.

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 re-wording seems necessary.

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.

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?
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.

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?

Results:
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.

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

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

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?).

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). 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.

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?

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.

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.

Discussion:
The discussion is somewhat unfocused and a bit superficial in its examination of the results. It needs a thorough revision.

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.

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.

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 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?

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.

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.

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.

**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