Author's response to reviews

Title: HIV, Hepatitis B and C among People who Inject Drugs: High prevalence of HIV and Hepatitis C RNA positive infections observed in Delhi, India

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Author's response to reviews: see over
To
The Editor
BMC Public Health
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Dear Editor,

Thank you very much for considering our paper for publication in your journal. We would like to thank the reviewers for their insightful comments that have served to improve the manuscript significantly.

We have revised the manuscript as recommended and have also provided a detailed point-by-point response for all comments. All changes in the manuscript have been highlighted for easy reference.

We hope you will find the revised manuscript suitable for publication. Once again, our sincere thanks to the reviewers.

Best regards,

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MAJOR COMPULSORY REVISIONS:

The logic in some of the conclusions from the data analysis is completely reversed and wrongly presented, which may lead to dangerous recommendations and considerations for programs focusing on prevention of HIV and HCV mono or co-infections: these conclusions that need compulsory revisions are the following:

- That accessing needle-syringe-program (NSP) services is an independent predictor for HIV-HCV co-infection

- That having comprehensive HIV knowledge is associated with a higher risk of HIV mono-infection, and HIV-HCV co-infection

- That any sex with a female partner, including unsafe sex was associated with lower risk

*We thank the reviewer for highlighting these very important points. We have undertaken further analysis to answer these questions more carefully. Our response to the first two points has been clubbed together.*

A more nuanced analysis is required to check on the associations of the three above mentioned factors with the other well recognized risk factors such as frequency and duration of injection.

Firstly, there should be an analysis on the profile of those who are reached by the NSP interventions. Most likely, considering need for selection justified target, cost or easy reach, Priority is given to those who are known in the area for a long duration and high frequency of injecting practice. This strong association would definitely show up in the regression analysis, but the main factor of risk remains the duration and frequency of injection - which most likely pre-determines the probability of being covered under the intervention. Since this is a prevalence analysis (and not incidence) it is also possible that the infection may have happened before access to NSP.

Secondly: The same logic also applies to the fact of having greater comprehensive knowledge of HIV. I assume that a multivariate analysis will show strong association between being part of NSP and having greater knowledge, which would add to the analysis in the paragraph above. if it is not the case, serious questions can be reached about the quality and non-effectiveness of NSP interventions in Delhi until a formal impact and effectiveness study is implemented. In addition, it is possible that for HIV positive PWIDs, the additional outreach by PLHIV networks for care and linkages to treatment may have improved that knowledge even if the infection
happened before the individual accessed prevention interventions. Comprehensive knowledge is proven in all literature to be a good enabler that reduces risk of infection.

We reviewed correlation coefficients for the key variables and also undertook further analysis. Comprehensive HIV knowledge and NSP use \((r = -0.02)\), duration of injecting drug use and NSP use \((r = 0.143)\), frequency of injections in the last 1 month and NSP use \((r = 0.412)\) were all poorly correlated and hence, we have retained HIV knowledge and NSP use in the model. Based on our analysis, we have added the following text to the section on multivariate multinomial regression.

Having comprehensive HIV knowledge was associated with a higher risk of HIV mono-infection (RRR: 1.5) and HIV-HCV co-infection (RRR: 1.47). Further, a higher likelihood of all three categories of infection was observed among participants who had accessed needle syringe program services in the last three months (HIV mono-infection RRR: 1.91; HCV mono-infection RRR: 1.37; HIV-HCV co-infection RRR: 1.74). These results are unexpected and need to be interpreted with caution. On further analysis, it was observed that comprehensive HIV knowledge increased with longer duration of injection use (<1 year: 27%; 2-5 years: 36%; 6-10 years: 41%; >11 years: 45%; \(p<0.001\)); the use of needle syringe program services also increased with longer duration of injection drug use (<1 year: 27%; 2-5 years: 44%; 6-10 years: 54%; >11 years: 53%; \(p<0.001\)) and frequency of injections in the last 1 month (no injection: 8%; 1-10 days: 48%; 11-20 days: 63%; 21-30 days: 62%; \(p<0.001\)). Among PWIDs who accessed NSP services, risky injection practices increased with frequency of injections in last 1 month (no injections: 1.92%; 1-10 days: 65.9%; 11-20 days: 76.9%; 21-30 days: 79.1%; \(p<0.001\)). However, comprehensive HIV knowledge was not associated with use of needle syringe programs services: 44% of participants with comprehensive knowledge and 46% without comprehensive knowledge had accessed needle syringe program services in the last 3 months (\(p=0.26\)). Public sector HIV prevention services delivered through Targeted Intervention (TI) programs for PWIDs in Delhi have been in existence for several years. PWID with longer duration of injections are more likely to be a part of the PWID community, and therefore, more likely to be covered by NSP and IEC services. PWID with a higher frequency of injections are more likely to seek NSP services due to a greater need for clean needles. However, PWID with longer duration of injecting and greater frequency of injections remain most at risk for new infections despite accessing NSP services as they may not obtain a sufficient supply of clean needles to meet their need, and continue to engage in unsafe injection practices as shown. Needle syringe distribution as part of our study was initiated only after completion of FV1.

Discussion section:

Accessing NSP services in the last 3 months was associated with a higher risk of HIV mono-, HCV mono- and HIV-HCV co-infections and having comprehensive HIV knowledge was associated with higher risk of HIV-HCV co-infection. These findings must be interpreted with caution. Further analysis showed that the use of NSP services and having HIV knowledge increased with longer duration of injection drug use, and higher frequency of injections. It is very likely that PWIDs who had been injecting for longer periods and were injecting more frequently were more aware of harm reduction programs in the area, had a greater need for needles/syringes and had been exposed to IEC activities in the area, and therefore, were accessing NSP services. At the same time, more than half the participants continued unsafe injection practices in the last one month, especially those who injected more frequently and accessed NSP services. It is possible that they are unable to obtain a sufficient supply of needles to meet their need. Thus, the main risk of infection remains rooted in unsafe injection practices, longer duration and more frequent injections. As this is a prevalence study we cannot comment on when the infections occurred; thus, it is also very likely that among
long duration PWIDs the infections may have occurred before participants started accessing NSP services.

Thirdly, there is a need to analyze the possible association between sexual activity and levels/frequency of drug intake, especially considering that 63% reported to be sexually inactive for the last 3 months, this would help understand the result showing that sexual activity means lower risk of infection. among drug users, these behaviors are not independent. It is known that high drug intake is associated to low libido leading to sexual inactivity. It is also well known that for PWIDs, the risk / probability of infection from drug injection is much higher than that form sexual activity. The logic is that high drug intake implies low or no sexual activity but leads to high risk of infection. at the same time, lower drug intake leaves room for some sexual activity (safe or unsafe) and means relatively lower risk of infection.

Sexual activity was also poorly correlated with duration of drug use ($r = -0.035$) and frequency of injections in last 1 month ($r = -0.085$), hence, we retained it in the model. We did find an association with duration of drug use and frequency of injections in last 1 month. We have added the following text.

Any sex (safe sex: RRR: 0.62 and unsafe sex: RRR: 0.40) compared to no sex was associated with a lower likelihood of HIV-HCV co-infection; unsafe sex (RRR: 0.60) was also associated with a lower likelihood of HIV mono-infection. In our cohort, only 37% of the participants were sexually active; sexual activity decreased with duration of injection drug use ($\leq 1$ year: 45%; 2-5 years: 36%; 6-10 years: 36%; $\geq 11$ years: 35%; $p=0.052$) and frequency of injections in the last 1 month (no injection: 41%; 1-10 days: 41%; 11-20 days: 35%; 21-30 days: 32%; $p<0.004$). Thus, given the small proportion of sexually active PWIDs, especially among long duration and more frequent injectors, the risk of HIV and HCV infection in our cohort was mainly concentrated around injection behaviors and not sexual behavior. Among the sexually active PWID, 70% (586/837) reported unsafe sex. Unsafe sex remains an important programmatic concern.

DISCRETIONARY REVISIONS:

in order to help the reader understand the vulnerability issues, it would be useful to develop the following aspects:

- It would be useful to clarify if the population council has implemented any intervention (NSP / prevention programme) in the context of this study, what proportion of the study population had prior access to the existing national interventions and for how long.

The harm reduction intervention, including NSP, delivered by the Population Council study was initiated only after participants completed FV1. Therefore, participants were accessing existing harm reduction services available through NACO’s targeted intervention (TI) program at the time of this data collection. Details on the proportion accessing these services are provided in table 1.

We have added the following sentence:

Needle syringe distribution as part of our study was initiated only after completion of FV1.
- what proportion of those accessing NSP still continue to engage in risky injection behavior.

_We have added the following text:_

Among PWIDs who accessed NSP services, risky injection practices increased with frequency of injections in last 1 month (no injections: 1.92%; 1-10 days: 65.9%; 11-20 days: 76.9%; 21-30 days: 79.1%; p<0.001).

- In results section, it is mentioned that HIV knowledge is low, provide value.

_We have provided the value._

- in the discussion, there is reference to HSS HIV prevalence, indicating that the study is finding higher level of prevalence than HSS, it would held to provide a brief discussion on the difference between the samples in terms of size (obvious) and geographical areas covered (HSS sites vs Study sites) - are they matching, overlapping, distinct?

_We have added the following text:_

The HSS is an annual exercise to monitor trends in HIV prevalence, and HIV testing is conducted among 250 PWIDs each at two DICs in Delhi; PWIDs are recruited through snowball sampling. One of the centers overlaps geographically with one of our study sites.

**Reviewer: Jagadish Mahanta**

- **Major and compulsory**
- As only about 25% of the study participants were from Delhi, the title of the Ms should be appropriately modified.

  _All the participants resided in Delhi and were recruited from hotspots and the community in Delhi. The regional classification refers to their state of origin. Hence, the title accurately refers to the prevalence among IDUs in Delhi._

- Authors may elaborate why they have taken HCV RNA positivity as the marker for prevalence of HCV in a cohort of IDU where many had history of injection for long time.

_We have added the following text under the laboratory testing._

We have considered HCV RNA positivity as the marker for HCV prevalence so that we could accurately identify active HCV infection and, therefore, IDUs who have the potential to transmit infection to others.

- In prevalence study involving long time IDU; HCV RNA detection at one point of time as marker for positivity will spuriously decrease the prevalence (L-128, 129).
Author may elaborate how they have accounted for those who had infection in the past due to injecting behaviour but became HCV RNA negative.

*The antibody test combines both IgM (marker of acute infection) and IgG (marker of past infection) antibodies, hence making it difficult to identify active and past (resolved) infections. HCV PCR tests following the total antibody test allows us to identify active infections. In this paper we set out to present the prevalence of current and active HCV infection.*

*We have reported both the antibody test results and HCV PCR results to show the difference in the proportions (lines 187-188 in original manuscript).*

HCV antibody tests were positive for 70.94% (1626/2294) of the participants; of those 75.65% (1230/1626) participants tested positive on HCV RNA PCR test, and were considered HCV positive.

• HBsAg estimation at one time is not a good marker for estimating the prevalence/exposure, when they get the infection in adult hood as a result of IDU behaviour. Hence the prevalence is gross under estimation. Author may add comment/explanation.

*We have provided the following explanation in the discussion section.*

Most studies have used HBsAg as the marker of HBV [8, 16]; it is possible that in the presence of a high prevalence of active HCV infection, all HBV infections may not be detected using HBs antigen testing. HBsAg is a marker of acute infection that persists during chronic infection. However, in some patients with acute infection (1-5%) and in the rare chronic low-level carrier, levels of HBsAg may be too low to be detected by standard assays and other tests may be required [29]. It is well documented that in dual infections, HBV and HCV interact, and affect immune responses. Available evidence demonstrates that the two viruses can inhibit each other simultaneously; the chronology of infection has a role in determining the dominant virus; and HBV and HCV can alternate their dominance [30-32]. However, the overall dominant effect in published literature appears to be HCV suppression of HBV. Furthermore, patients with chronic HCV may have occult or silent HBV infection with low levels of circulating HBV DNA, and lack the HBsAg and HBeAg markers and their antibodies [30, 33]. Undetected HBV is a concern as the virus can be transmitted through percutaneous, sexual and mother-to-child routes. Future studies should consider using a wider panel of tests to determine HBV prevalence in this high risk population, as a one-time HBsAg test may underestimate prevalence.

• HIV negative cases were retested for HIV again at FV1. Authors should add a statement of HIV conversion during this period.

*A total of 113 HIV seroconversions took place between baseline and FV1 over a cumulative 1,399.2 person years of follow-up, resulting in an incidence rate of 8.1 per 100 person-years (95% CI: 6.7-9.7). This has been published in a previous paper (Sarna et al. 2014)*

*We have added the following sentence, pertaining to this sample (n=2292).*

HIV prevalence was 25.9% (595/2292); this includes the 109 new seroconversions documented between baseline and FV1.
• Authors have taken the behavioural information at FV1 stage. Since all the subjects were interviewed at FV1 stage, the data on behaviour study were influenced and elements of bias. Authors may elaborate how such bias was addressed.

    Our apologies, we have not understood this comment; hence have not been able to address it. We will be happy to respond.

This is a cross-sectional assessment and the behavioural and biological indicators were collected at the same time. To the best of our understanding this would not create a bias. There may be the issue of participants having participated in the baseline survey, but we think that the long gap between surveys would prevent/ minimize any bias. The median duration between baseline and FV1 was 9.8 months (IQR: 8.2-11.1 months)

• Authors could detect duplicate data in baseline and FV1 (L-160,161). Author should elaborate in material and methods about the identifiers used to avoid such duplicate sampling. Author should also indicate the interval between the baseline data collection, FV1 and FV2.

    We have added the following text in the revised manuscript.

To detect duplicate registrations at recruitment, we used a web-based, live data-base accessible by all five DICs which allowed the DIC site manager to verify new clients against already registered clients. Registration procedures included the recording of photographs and the following identifiers: name, age, gender, marital status, height, weight and fore-arm length – participants presenting with similar identifiers were identified by the computer program for further scrutiny against their photograph (Tun et al. 2014)

    We have added the following information in the methods section.

The median follow-up time between baseline and FV1 was 9.8 months (IQR: 8.2-11.1 months), and between FV1 and FV2 was 12.0 months (IQR: 10.7-13.2 months)

• Though the authors have shown follow up till FV1 but are silent about the drop out or loss to follow up after FV2 from initial 3740 subjects registered at baseline. They should also mention about the FV2 status of the subjects (behaviour and laboratory test)

    A total of 2585/3748 (68.9%) male IDUs returned for the FV2. We have mentioned this in a footnote under figure 1, but would like to suggest that we do not include this information as we are presenting findings (HIV, HBV and HCV) from FV1 in this paper. We believe adding behavioural and laboratory data from FV2 is beyond the scope of this paper. We are presenting HIV incidence in another paper that refers only to the HIV negative cohort.

• Since the samples were collected from rehabilitation and residential care centres passively, there is a possibility of gross under reporting for prevalence of
HIV, HBV and HCV.

*Our study participants were recruited from the community and hotspots and recruitment continued till we could not find any new IDUs at these hotspots. The recruitment strategy has been described in the next section.*

*Participants received services at Drop-in Centers that operated during the day and were not residential facilities, and samples were collected at laboratories set up in the DICs. Thus, the prevalence reported is for a large cohort from the community and we believe it reflects the actual prevalence in the population.*

- Authors may elaborate, why they have chosen to test for HIV RNA or HCV RNA only at FV1 stage, not at base line or FV2.

*We would have definitely liked to undertake HCV testing at FV2; unfortunately we could not do so as we did not have funds for a second round of testing. This has already been mentioned in the manuscript under the limitations (lines 302-305 in original submission). We have highlighted the text for easy reference.*

- Samples appear not to be representative of the IDU population. A detail note on sample recruitment should be added in the Ms

*As recommended, we have added the following paragraph on recruitment procedures.*

Participants were recruited through peer-referral and targeted outreach by outreach workers (ORW). Prior to study initiation, a mapping exercise was conducted to identify all hotspots where IDUs congregated in central, east, north-east and north-west districts of Delhi where the five Sahara Drop-in Centers were located. The peer-referral recruitment process was initiated using eleven ‘seed’ participants (recruiters) across the five study sites; each ‘seed’ participant was provided with five recruitment coupons to give out to IDUs in their network. New recruits were linked to the recruiter through unique ID numbers; each new recruit received five coupons to recruit other PWIDs and the recruiter received a ‘food coupon’ for each new PWID s/he brought into the study. Food coupons were exchanged for food at selected restaurant outlets. For recruitment using targeted outreach, ORWs visited hotspots to invite PWIDs to participate in the study and willing IDUs were directed to the study site with an ORW coupon. All PWIDs who had a peer-referral recruitment coupon were considered recruited through peer-referral while those who came to the site with an ORW coupon were listed as recruited by ORWs. Walk-in clients who did not have either a peer-referral or ORW coupon were also permitted to enroll. All PWIDs who enrolled in the study, including walk-in clients and those recruited by ORWs, received five recruitment coupons each to recruit other PWIDs. Every hotspot was covered during the recruitment phase and recruitment continued till no new IDUs could be found. To be eligible, participants had to be 18 years of age or older, current IDU defined as injecting at least once in the last 3 months and residing in Delhi. All participants provided written informed consent. All participants received Rs 40 (approximately 80 US cents) for participating in the behavioral survey.

- Authors have not mentioned about period of follow up and the time interval between baseline sampling, FV1 and FV2 tests. Authors may add it in methodology.

*We have added the following information in the methods section.*

The median follow-up time between baseline and FV1 was 9.8 months (IQR: 8.2-11.1 months), and between FV1 and FV2 was 12.0 months (IQR: 10.7-13.2 months)
• Table-1 Age-29 (what is 29?). Column 2 should have proper legend

*Age 29 is the median age. The variable has been described in column 1: Age (median, IQR)*

• Table-2 Duration of injection >2 yrs will have recall bias

*We have stratified duration of injection drug use as reported in BSS 2006.*

• Minor Essential Revisions

• Recruitment through peer referral, TORW and walk in clients may not yield the representative population for prevalence study. Less effort in recruitment might have resulted in lesser number of female IDU for the study. Author may add their comment.

We have added this text under the limitation section

Despite using multiple strategies to reach female PWIDs including female seeds for peer-referral and female out-reach workers, we were able to recruit only 26 female IDUs. In our previous study in 2006, we used respondent-driven sampling and were able to only recruit 17 female IDUs [reference]. It is very likely that there are few female IDUs in Delhi. This finding has also been reported from other parts of India and in Asian countries [19, 32]. Anecdotal information from ORWs in Delhi suggests that non-injecting drug-use is more frequent among female drug users; further research with female non-IDUs is needed to better understand drug use in this population.

• Author should elaborate the phrase “Majority are not sexually active” with how many of them were married, physically fit or separated due to rehabilitation and residential care in this group.

• Authors may elaborate about follow up 2 stage and the drop out at that level.

• It is not clear why authors have chosen only HIV at baseline, HIV, HBV, and HCV in FV1 and have not given any information about FV2 as planned earlier. Even there is no mention in the flow chart.

*As we are presenting findings (HIV, HBV and HCV) from FV1 in this paper, we believe adding behavioural and laboratory data from FV2 is beyond the scope of this paper. We are presenting HIV incidence in another paper that refers only to the HIV negative cohort.*

• As the study participants were from Delhi, adjoining states and other states (L-143,144), authors should show the result separately.

*As explained above, all the participants were residing in Delhi and were recruited from the community and hot spots in Delhi. Regional origin refers only to their place of origin.*
• Fig-2. Data shown as % and depicted as bar gives a false impression. Authors may appropriately modify it

*We have removed the figure and provided information in the text (highlighted)*

• Discretionary Revisions

• Statement like “High prevalence among Hindus” is misnomer in absence of representation in sample or in population. Hence this may be omitted.

*Omitted*

• Access to detox, rehab services were only 5.89% or to OST 10.73%. What was the effort from investigator to increase attendance to such services after they were registered in rehabilitation and residential care centres?

*Out-reach workers and DIC staff encouraged clients and provided referrals for OST services provided at government supported centers.*