Author's response to reviews

Title: Acceptability and implications of the rapid hepatitis C screening test among high-risk young people who inject drugs

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Dear Dr. Zule,

We thank the Editors and Reviewers at BMC Public Health for the thorough and helpful review of our manuscript “Preference, acceptability and implications of the rapid hepatitis C screening test among high-risk young people who inject drugs”. The comments and suggestions have substantially improved the manuscript. Below we provide enumerate the reviewers comments and our corresponding responses, and indicate where the changes have been made in revised manuscript. We are hopeful that this revised paper will meet the Editors’ expectations and be suitable for publication. Please do not hesitate to contact me with any questions or clarifications.

Response to comments:

Reviewer 1: Ann Drobnik

1. The last paragraph of the background section needs to more clearly communicate your objective. In the statistical analysis paragraph you state that your main outcome of interest was which test participants chose, however, the background section and your title seem to indicate that your main interest was in the acceptability of the rapid test. From this paragraph and the results section, it seems like you were looking at test choice only to assess whether or not persons who chose the rapid test were different from those who chose the blood draw. The final paragraph of the background section has been revised to more clearly describe the intent of the study as 1) measuring preference for rapid vs. standard testing based on choice of test and 2) levels of acceptability of the rapid test based on a questionnaire. This section is congruent with the methods and primary result stated in the first paragraph of the Results section.

2. In general in the background section you need to make a stronger case for why and how young PWID may be different from other PWID and therefore worth studying. This could also be strengthened in the discussion. The second paragraph of the background section has been revised describing HCV among young PWID and making the case that young PWID are at increased risk of HCV.

3. It’s not clear what data was collected from the outcomes questionnaires of persons who chose phlebotomy testing. There are some data presented for the first time in the 1st paragraph of
the discussion that are not in the tables or presented in the results and seem to indicate that you collected additional data from this group that wasn’t shown previously. The methods, results, tables and discussion have been revised and clarify what data was collected. As this is an ongoing prospective observational study, all participants are asked to participate in regular baseline and quarterly data collection, which queries for demographic, risk exposure and other health factors. A separate survey was also administered for this sub-study, which queried participants regarding the rapid tests.

4. The second to last paragraph of the paper you note that the study is limited by the fact that participants were already engaged in a study of HCV transmission and risk, but based on your sampling method paragraph, I understood that participants had also agreed to be periodically tested. This is the real limitation because the advantage of the rapid test is that it may encourage persons who wouldn’t test otherwise to get tested. This should be discussed if my understanding of the agreement to test is correct.

We have added this information (that the sample has already agreed to testing) to the limitations paragraph of the discussion section.

5. A sentence or two explaining why the risk of HCV acquisition is especially high in this group as compared to other age groups, and information on trends over time in this group would make a stronger case for why this is an important demographic group to focus on for HCV testing.

Paragraph 2 of the Introduction now explains the exceptional risk of young PWID and trends over time.

6. In paragraph 2 you state that identifying acute HCV is important, however, the rapid test cannot necessarily detect acute HCV so this statement seems out of place in the background section. It may be better as a point of discussion at the end in pointing out the limitations of the rapid test where you bring up the need for RNA testing.

Paragraph 5 of the discussion section now elaborates on the limitation of anti-HCV antibody testing, and paragraph 6 makes the case that the rapid test could potentially offer providers a window to identify when people might have been infected, without saying that it could be used to specifically diagnose acute infections.

7. On page 5 in the first paragraph of the methods section, specify that the HCV rapid test is a finger stick.

The first paragraph of the methods section now specifies that the HCV rapid test involves a finger prick.

8. On p. 5 in the first paragraph of the methods section, please explain what a rapid test disclosure is.

The first paragraph of the methods section clarifies the process of the disclosure of a rapid test result.

9. On p. 5 in the first paragraph of the methods section, were participants all recruited from baseline of the UFO study, or were they approached at follow-up visits as well? The second sentence made me think the former, but then a couple of sentences later data collection at baseline and follow-up visits is mentioned.

The first paragraph of the methods section clarifies that data was collected from newly enrolled participants at baseline, and some participants who were returning for follow-up visits.
10. On p. 5 in the first paragraph of the methods section, you indicate that subjects must self-report negative HCV RNA – you need more explanation for how this was asked/ascertained. Were persons with unknown HCV status eligible? Were persons with a previous negative antibody test eligible? Were persons with a previous positive antibody but negative RNA eligible?
The first paragraph of the methods section now stipulates that eligibility for participation included people whose self-report status is unknown, or anti-HCV positive and HCV RNA negative.

11. The last sentence of the first methods paragraph – the word choice of “perfunctory” is a little confusing. Does this mean that participants got a blood draw at each visit as per the standard protocol for the UFO study whether or not the individual chose to participate in the rapid test portion of the study?
Yes: Participants received blood draws for HCV RNA testing irrespective of anti-HCV testing method, and therefore can be considered perfunctory. For clarity, we changed this word choice to “routine”.

12. In the second paragraph of the methods section (measures) there are several measures listed which do not appear in your tables (age of first injection, incarceration history, some service utilization measures). You should either exclude them from the methods, or present them in your table and comment on the findings in the results section.
The Measures paragraph of the Methods, paragraph 2 of the Results, and Table 1 are now congruent, reflecting data about: (a) sociodemographic information including age, race/ethnicity, gender, any homelessness in the past 3 months; (b) previous HIV testing history and self-reported anti-HIV status; (c) service utilization, including having used a needle exchange past 3 months; and (d) number of years injecting. Paragraphs 2-4 of the Discussion now make more thorough comments on these findings.

13. In the statistical analysis paragraph, you don’t need to repeat the measures that you looked at unless you did distinct analysis on particular variables. These should be listed only in the measures paragraph.
Repetition of measures between the Statistical Analysis paragraph and the Measures paragraph has been eliminated. Measures are now only stated in the Measures paragraph.

14. As in the measures section, in the statistical analysis section you need a separate paragraph devoted to the methods that generated table 2. As is, it reads as though you used chi square to look at the survey outcomes measures, but since these questions were restricted only to those who chose the rapid test, the analysis for these data need to be explained separately. It’s also confusing that you’re referring to the table 2 findings as the “survey outcomes”, when these aren’t the stated outcomes of interest of the study.
We revised the language in the methods section by clarifying our description of Table 2 by: (a) making reference to the frequencies generated to display results from the 'rapid HCV test survey' found on page 9; and (b) by removing any reference to 'survey outcomes' and changing the language to 'measures', which can be found on page 10.

15. Fishers exact test may be more appropriate for comparing differences between the two testing groups as you have a very small sample size of persons who chose the blood draw.
We note in the methods and tables that Fishers’ exact test was used to compare groups with small numbers.

16. Table 1 – why not break down the non-white category?
Table 1 now breaks down the non-white category.

17. Table 1 – It’s counter intuitive to have the first column of the total sample adding to 100% going down the rows, while the second column of rapid test takers adds to 100% going across and adding that column to the missing phlebotomy column. Suggest restructuring it so that by adding the rows going down rather than across you arrive at 100%, showing the phlebotomy column to make the numbers much more meaningful, and adding p-values
Table 1 has been revised. We removed the proportions describing the study sample. We added a column to include the number and proportion of participants who elected phlebotomy. We retained row percents as the principal purpose of this table is to present the probability of the outcome (rapid test) given the characteristic. The addition of the new column shows the entire sample (adding to 100%).

18. Table 2 – suggest being consistent with table 1 and showing both N and %, with just 1 decimal place.
Tables have been revised to be more consistent as suggested.

19. In the results section, paragraph 2, you state that there were no significant differences in participant characteristics between those who chose the rapid test and those who chose the phlebotomy. First, table 1 doesn’t show the data for the phlebotomy participants so readers aren’t able to look at these results, and second, it’s not clear whether or not there were differences on the other measures (service utilization or risk behaviors). Because you list participant characteristics as separate from service utilization and risk behaviors in the methods it’s important to explicitly state any differences or the lack thereof, particularly if the data are not shown in your table.
Table 1 and paragraph 2 of the results section has been revised to show data reflecting differences between testing choice by different group characteristics.

20. You do a nice job in the measures paragraph to label the 3 types of measures you collected as a-c, making it very easy to follow. Be consistent when you refer to these three groups of measures in the results and in the discussion (first paragraph). As stated above, some of the measures are left out of the results section, and in the discussion the language isn’t consistent.
Paragraph 2 of the results section and paragraph 1 of the Discussion have been revised to use consistent language in discussing measures of the sample characteristics.

21. In the results, it would be helpful to say a bit more about who the young PWID population in your sample is and in the discussion to contrast them with the literature about PWID generally. For example, a large majority of your sample was homeless in the previous 3 months. Are most PWID homeless, and if this is something that is more common among young injectors, might this be a reason given the instability and transitory nature of homelessness to offer a testing method that doesn’t require the patient to come back for results?
We have included additional discussion regarding the sociodemographic characteristics of the sample, with some comparisons to other studies of young adult PWID (Discussion section; page
2) We agree that unstable housing and other transitory characteristics of young adult injectors in the UFO sample may be a good reason to offer rapid testing.

22. In the discussion, paragraph 2, please explain why RNA testing is necessary and emphasize that for sites that don’t have phlebotomists on staff or cannot cover the cost, referrals must be provided to persons testing antibody positive.

Paragraph 7 of the Discussion discusses the need for RNA testing to confirm actual infection. Since some proportion of people clear HCV infection spontaneously, we provide participants with information about actual infection. We note that different systems, including referrals and training will be necessary if test results are limited to just anti-HCV results.

Discretionary revisions

1. On p. 5 in the first paragraph of the methods section, state what CLIA is, why its required for rapid testing

In the methods section, the sentence mentioning CLIA was amended to include information regarding this regulatory requirement (by FDA and CDC).

2. On page 5 in the first paragraph of the methods section, “participants participating” (line 3) doesn’t flow well. Suggest rephrasing to avoid using these two words together.

This has been revised as suggested.

3. On p. 5 in the first paragraph of the methods section, be consistent with the use of report and self-report (injected in the last 30 days, negative HCV RNA)

The first paragraph of the methods section was edited to be consistent with the use of “self-report.”

4. On page 5 in the first paragraph of the methods section: specify that the pre- and post-test risk reduction counseling is specific to HCV risk. It follows a sentence about phlebotomists having HIV rapid test counseling experience, but not HCV so it’s not clear that the counselors are trained in HCV risk reduction specifically.

The second paragraph of the first section (Study Population and Data Collection) of the methods section was edited to clarify this.

5. The last sentence of the measures paragraph in the methods section explaining why these measures were collected should come before the explanation of the measures themselves.

This has been modified as suggested; moving the explanation of measures to precede the description.

6. First sentence of the 3rd paragraph under discussion, change to “this test offers a critical opportunity to increase HCV testing AMONG high risk young PWID”

The first sentence of paragraph 6 (formerly paragraph 5) was modified as suggested.

Reviewer 2: Daniel Church

1. One major issue is regarding test results and RNA testing. It is not clear from the methods what happened to those that were found to be HCV ab+. The article states that RNA testing was "perfunctory" but I am not sure that is the right word. This is confusing and an important component to clarify. Not only access to RNA testing, but then what was the timeline with results?

We revised the methods section (first section: Study Population and Data Collection) to more clearly describe this. As noted above in response to Reviewer 1, we also indicate what was "routine" (rather than perfunctory), as well as the timeline for results.
2. While the focus in this paper is not on the results of the testing given the primary interest in acceptability, it may be relevant to explore if those testing positive felt different about the testing than those who were negative. For example, if a participant testing HCV ab+ by rapid test, they then would need to have a blood draw as well (and therefore a fingerstick and blood draw). If the testing was all standard serology, only one blood draw is needed with reflex to RNA testing for those that are ab+. In order to fully capture the response to the test methodology, it would be helpful to explore this.

Perceptions regarding the rapid test did not differ by serostatus (noted in the results section; page 10) and discussed in the first paragraph of the Discussion (Page 12). We also note that all participants had other types of serological data collection in addition to finger-prick. This is discussed in the limitations section.

Minor Essential Revisions:
1. Estimates on HCV prevalence included in the Background have recently been updated from NHANES data and those updated results should be used. Estimates on HCV prevalence in the background section have been updated using new NHANES-based data.

2. The authors mention the importance of testing for and identifying acute HCV infections, however, that can not be accomplished with the rapid HCV antibody test so it does not seem a directly relevant point. Since acute HCV infection is more of a clinical diagnosis with NAT testing it would be very unlikely to occur in the settings targeted for rapid HCV antibody testing with non-clinical staff.

We discuss this issue further in the discussion section (see page 15; limitations), and now elaborate on the limitation that the rapid test cannot determine acute infection status. We include the point that there may be limitations in some settings regarding follow up for HCV RNA testing. We do, however, think that it is important to emphasize the need for HCV RNA testing as part of all HCV testing, especially among PWID. As the combination of anti-HCV and RNA testing can identify acute infections, and since this is a period of high viremia during which PWID may be potentially transmitting infection, we still note the need for conducting both tests.

3. There is no mention in the background of greatly improved HCV treatments that can cure HCV infection. It seems that this is a critical point to address given that access to care and treatment are one of the primary reasons for conducting HCV testing.

Paragraph 4 of the Background now addresses improved HCV treatments and the importance of how testing is critical to increasing access to effective treatment.

4. The authors compare rapid HIV testing to rapid HCV testing in the background but do not mention the difference between these tests in that an HCV+ test result does not always equate to current infection status as it does with HIV.

Paragraph 5 of the Introduction (page 4) now discusses new treatment options and the potential to increase access to care for PWID and increase demand for faster, more accessible testing options.

5. In the methods, the authors indicate that the participants all self-report being negative for HCV RNA. This suggests that the study population have all been previously tested for HCV RNA and likely HCV antibody. While it is fine to assess this group for the acceptability of this test, and they may have useful insights, it should be stated that this is a limitation of the research in terms of applicability to other populations.

We clarify in the Methods that participants also may report “unknown” HCV serostatus. We also discuss (page 13) this in the limitations section.
6. A minor point, but it would be good for the authors to use decimals consistently - most of the results only go out to one decimal point, and that should be done throughout the paper, especially given the limited number of participants.

This edit has been made.

7. In the Discussion, the authors mention that there is a "high" preference for the fast results - since it was only 60%, I think removing the work "high" from that sentence would be appropriate.

“High” has been removed from the sentence regarding fast results.

8. At the end of the first paragraph of the Results, the authors use the percentage of the standard test takers - it would be useful to include the number here too since it was a limited number of participants.

Numbers now accompany percentages in the results section.

9. At the end of the second paragraph there is reference to the "inconvenience of a painful finger-prick" although this appears to be in relation to RNA testing, so isn't it a standard blood draw that they are comparing the possibility of blood spot testing to?

Paragraph 1 of the Methods clarifies that the rapid test uses a finger-prick. Paragraph 1 of the Discussion discusses the results shown in Table 2 that some participants found the finger-prick more painful than the phlebotomy blood draw of standard testing. Paragraph 5 of the Discussion discusses that there are no alternatives to the finger-prick for rapid testing, so that may be a deterrent for some individuals. Phlebotomy may be avoided in RNA testing with a dried-blood spot; this is mentioned now in Paragraph 7 of the Discussion.

10. The discussion has excellent discussion on how HCV testing is an important component of HCV prevention among PWID. The detail included here was thoughtful and important. However, the authors should strengthen the text regarding that testing is also a key way to engage people in HCV medical care. "Linkage to care" is mentioned, but access to medical care is one of the primary reasons that HCV testing can be useful. While there is no evidence currently for how well the rapid test peforms as a means of getting people into HCV medical care, this issue should be discussed in more detail in this section.

Paragraph 6 of the Discussion is now more explicit about the value of testing to improve linkage to care.

11. The final paragraph of the discussion states that rapid HCV antibody testing does not require phlebotomy or accessible veins - clearly two important qualities of this test with this population. However, while the rapid HCV ab test does not require phlebotomy, if someone tests ab+, phlebotomy is currently required so it is more that such skills, and accessible veins, are not initially required. I would also recommend saying that "...and MAY streamline access to care and treatment..." as it is not know how well this test succeeds at engaging young PWID in care.

The final paragraph has been edited according to this suggestion.

Again, we thank the reviewers and the Editors for their helpful input.

Regards,

Kimberly Page