## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | A prospective cohort study characterizing the role of ano-genital warts in HIV acquisition among men who have sex with men-a study protocol |
| **AUTHORS** | Brown, Brandon; Davtyan, Mariam; Leon, Segundo; Sanchez, Hugo; Calvo, Gino; Klausner, Jeffrey; Galea, Jerome |

## VERSION 1 - REVIEW

| | |
|---|---|
| **REVIEWER** | Garrett Prestage<br>University of New South Wales |
| **REVIEW RETURNED** | 03-Jul-2014 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is a well-conceived and comprehensive study design, and it is described well in this paper. Nonetheless, there are some points that require some attention.<br><br>The word 'data' is plural.<br>The authors have failed to note whether the physical examinations for both HIV and HPV (and AGW) occur at all follow-ups as well as at baseline. Presumably that is the case for HIV, but if it is also the case for HPV, then would it not also be possible to include HPV & AGW incidence as additional outcomes?<br>Presumably, incident HPV & AGW would also be associated with HIV infection. Has this been addressed in the power calculations? If HPV (& AGW) incidence is not being measured and HPV testing only occurs at baseline, then this would appear to be problematic.<br>The authors specify that they will be investigating the association between AGW and HIV in Peru. Presumably, any biological associations would be similar, regardless of location. However, I imagine there may be clinical and social circumstances that would mean that there may be differences between the situation in Peru and what has been found elsewhere. If so, it may be worth mentioning these.<br>Where will the survey completion occur - on site in the clinic, or elsewhere? Will it occur before or after the physical examination? Will it be self-completed by participants or will the questionnaire be administered by someone else (who)? What measures are taken to ensure both the appearance of and actual confidentiality?<br>The authors state they expect a 13% loss to follow up. What is the |

| | |
|---|---|
| | basis for this expectation? |

| | |
|---|---|
| **REVIEWER** | Huachun Zou<br>University of New South Wales, Australia |
| **REVIEW RETURNED** | 05-Aug-2014 |

| | |
|---|---|
| **GENERAL COMMENTS** | While this is an interesting study, it needs further revisions for it to be considered to be accepted on BMJ Open. I have the following suggestions:<br><br>1. In the title, please add “anal” before “genital” as the study will include MSM with anal and/or penile warts.<br>2. Among the 300 men with warts, how many men with anal warts, men with genital warts, and men with anal and genital warts are you going to recruit? Or you will see how it goes? Why?<br>3. Please clearly state at each visit what sample from which anatomical site, what questions are you going to collect.<br>4. As you are following men for 4 times over 2 years and test for 37 HPV Why not have an analysis of the incidence and per partnership or per action transmission probability of HPV of each type among MSM, stratifying warts status.<br>5. In the statistical methods section, “Fisher exact test” may not be suitable to analyse binary variables if the sample is big as it gives more conservative estimate. You might want to use normal chi square test to analyse binary variables and fisher exact test when sample is small for certain variables.<br>6. In figure 1, the legends may be wrong as you are testing STIs for HIV positive men? From the current flowchat, it seems every men will end up becoming HIV positive but this may not be the truth. Please modify the flowchat to make sense.<br>7. This manuscript needs proofread by an English language expert or native English speaker. In quite a few places it doesn’t read very well. For example: line 24 page 7, “The Gay Men’s~~~ (unpublished data)”; line 34 page 7, “similar data for Peru” should be changed to “data on HPV in MSM in Peru”; line 44 page 7, “HPV” should be changed to “AGW”; line 27 page 6, “men who~~disease” should be changed to “populations heavily burdened by HPV-related diseases such as MSM and TGW”.<br>8. Please use lower case for first letter for syphilis, chlamydi, gonorrhea, trichomonas throughout paper.<br>9. Some sentences are repetitive. Please reorganise so you do not repeat the same information again and again. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name Garrett Prestage
Institution and Country University of New South Wales
Please state any competing interests or state 'None declared': None declared

This is a well-conceived and comprehensive study design, and it is described well in this paper. Nonetheless, there are some points that require some attention.

The word 'data' is plural.
RESPONSE: Thank you. Instead of 'This data' we have written 'these data'

The authors have failed to note whether the physical examinations for both HIV and HPV (and AGW) occur at all follow-ups as well as at baseline. Presumably that is the case for HIV, but if it is also the case for HPV, then would it not also be possible to include HPV & AGW incidence as additional outcomes?
Presumably, incident HPV & AGW would also be associated with HIV infection. Has this been addressed in the power calculations? If HPV (& AGW) incidence is not being measured and HPV testing only occurs at baseline, then this would appear to be problematic.
RESPONSE: Thank you for pointing this out. We have specified that physical examinations occur at each study visit in the manuscript. While we currently only have funds to test for HPV DNA at one time point, we collected samples at each visit and hope to obtain funds for this testing in the future. We agree this is less than ideal but we face monetary constraints. We have specified that HPV samples are collected at each visit. AGW incidence is measured at each study visit during the physical exam. We have included this in the manuscript.

The authors specify that they will be investigating the association between AGW and HIV in Peru. Presumably, any biological associations would be similar, regardless of location. However, I imagine there may be clinical and social circumstances that would mean that there may be differences between the situation in Peru and what has been found elsewhere. If so, it may be worth mentioning these.
Where will the survey completion occur - on site in the clinic, or elsewhere? Will it occur before or after the physical examination? Will it be self-completed by participants or will the questionnaire be administered by someone else (who)? What measures are taken to ensure both the appearance of and actual confidentiality?
RESPONSE: Thank you for this comment. We are not aware of similar studies which have examined the association between AGW and HIV (apart from reference 8), but we have referenced several studies which examine the HIV/HPV association. We have added our recent review paper on HIV and HPV in MSM to the references. The survey will be administered at baseline following the physical exam to examine for ano-genital warts to ensure that we collected 300 participants in the AGW arm and 300 participants without AGW. At each subsequent visit, the survey was collected prior to the physical exam and any testing. We have added information specifying that the survey was filled out by the participant in a private area. No personal identifiers were collected.

The authors state they expect a 13% loss to follow up. What is the basis for this expectation?
RESPONSE: This loss to follow-up was estimated from previous longitudinal studies of MSM at the study site, Epicentro, which estimated 10% loss to follow up. In another longitudinal study in Peru of a high risk group (female sex workers), loss to follow-up was only about 5%, but this is another population. We believe our estimate is conservative.

Reviewer: 2
Reviewer Name Huachun Zou
Institution and Country University of New South Wales, Australia
Please state any competing interests or state 'None declared': N/A

While this is an interesting study, it needs further revisions for it to be considered to be accepted on BMJ Open. I have the following suggestions:

1. In the title, please add "anal" before "genital" as the study will include MSM with anal and/or penile warts.
RESPONSE: We have modified genital to be 'ano-genital' to show this includes both types of warts.

2. Among the 300 men with warts, how many men with anal warts, men with genital warts, and men with anal and genital warts are you going to recruit? Or you will see how it goes? Why?
RESPONSE: Thank you for this question. We did not plan to enroll a specific amount of participants with different types of ano-genital warts. All individuals with ano-genital warts include anal, penile, or scrotal warts.

3. Please clearly state at each visit what sample from which anatomical site, what questions are you going to collect.
RESPONSE: Thank you for this comment. We have added this detail to the manuscript.

4. As you are following men for 4 times over 2 years and test for 37 HPV Why not have an analysis of the incidence and per partnership or per action transmission probability of HPV of each type among MSM, stratifying warts status.
RESPONSE: Thank you for the excellent suggestion. Due to limited funds, we only are able to perform HPV DNA testing at one time point (baseline). We hope to attain additional funds to test the swabs for HPV DNA at subsequent visits and be able to look at HPV incidence. We will test serum for HPV antibodies at baseline and the final visit as mentioned in the manuscript.

5. In the statistical methods section, "Fisher exact test" may not be suitable to analyse binary variables if the sample is big as it gives more conservative estimate. You might want to use normal chi square test to analyse binary variables and fisher exact test when sample is small for certain variables.
RESPONSE: Thank you, we agree and have made this change in the text.

6. In figure 1, the legends may be wrong as you are testing STIs for HIV positive men? From the current flowchat, it seems every men will end up becoming HIV positive but this may not be the

truth. Please modify the flowchat to make sense.
RESPONSE: Thank you, we have modified the flowchart to make sense.

7. This manuscript needs proofread by an English language expert or native English speaker. In quite a few places it doesn't read very well. For example: line 24 page 7, "The Gay Men's~~~ (unpublished data)"; line 34 page 7, "similar data for Peru" should be changed to "data on HPV in MSM in Peru"; line 44 page 7, "HPV" should be changed to "AGW"; line 27 page 6, "men who~~disease" should be changed to "populations heavily burdened by HPV-related diseases such as MSM and TGW".
RESPONSE: We apologize and thank the reviewer for his comment. The 4 native English speaking authors use American English, and we have attempted to clarify when needed. We have tried to modify the document as you described.

8. Please use lower case for first letter for syphilis, chlamydi, gonorrhea, trichomonas throughout paper.
RESPONSE: Thank you for pointing this out. We have made this change throughout.

9. Some sentences are repetitive. Please reorganise so you do not repeat the same information again and again.
RESPONSE: Thank you for the comment. The STROBE checklist requires some repetition in this document, with similar information required in different sections. We have made the changes possible to avoid repetition.