Author's response to reviews

Title: Twelve-month incidence and clearance of oral HPV infection in HIV-negative and HIV-infected men who have sex with men: the H2M cohort study

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

Thank you for considering our paper "Twelve-month incidence and clearance of oral HPV infection in HIV-negative and HIV-infected men who have sex with men: the H2M cohort study" for publication in BMC Infectious Diseases. We are grateful for the opportunity to benefit from the valuable input given by the reviewers. Most importantly, we added more information to the Introduction on what is known of the natural history of oral HPV infection. In this letter, we indicate how we dealt with each of the comments of the reviewers. We hope that the revised version of the manuscript will be accepted for publication in BMC Infectious Diseases.

Reviewer 1:

C: Discretionary Revisions

The conclusions fit well with the experimental findings and your main goal (comparing the 12-month incidence and clearance of oral high-risk HPV infection between HIV-infected and HIV-negative MSM) has been reached. Concerning the determinants of incidence and clearance rate, some other investigations could have been made, for instance:

1) Have you examined the role of immune function and HIV-RNA in relation to higher or lower rates of HPV incidence/clearance?

R: We included nadir CD4+ count in uni- and multivariable analyses of determinants of incident oral high-risk HPV infection (Table 2). We did not include CD4+ cell count at enrolment and HIV viral load because we have previously experienced a lack of power due to the overall high CD4+ cell count and the very high proportion of participants with undetectable viral load in the HIV-infected study population. For the analysis of clearance, we were not able to stratify the analyses by HIV-status (page 8, lines 159-161) and therefore, CD4+ cell count or viral load were not included in uni- and multivariable analyses.

We have now added more information about the immune status of the HIV-infected population (page 9, lines 180-182). We also added information about variables, including nadir CD4+ cell count, that were not associated with HPV infection (page 10, lines 198-202 and lines 213-215).

2) You could also try to stratify HIV+ patients in relation to HCV or HBV co-infection status (e.g. you could refer to the article "Oral human papillomavirus detection in older adults who have human immunodeficiency virus infection", Fatahzadeh et al, 2011).

R: We were not able to conduct these analyses, because we did not collect data on HCV and HBV co-infection.
3) Some recent evidence found that oral health (ulcers, gum disease, chronic inflammation, number of lost teeth) could be a risk factors for oral high-risk HPV infection irrespective of smoking and oral sex practices (see “Examining the association between oral health and oral HPV infection”, Bui et al, 2013 or “Oral human papillomavirus infection and its risk factors among 5410 healthy adults in China, 2009-2011”, Dong Hang et al, 2014). Were there any questions about oral hygiene in the risk factor questionnaire? Did the patient undergo a stomatologic assessment? If such observations have not been taken into consideration, they could be a suggestion for further investigations, in order to better understand which patients groups are mostly at risk of HPV infection and persistence.

R: Thank you for this important suggestion. Unfortunately we did not collect data on oral health, and neither was a stomatological examination done, so we could not include this in our analysis. We added the suggestion to include oral health in future natural history studies to the Discussion (page 12, lines 266-268).

Reviewer 2

Thank you for an interesting article on the natural history of oral HPV in HIV MSM.

C: Major compulsory revisions
Introduction seems quite brief and doesn’t give enough background information. Please reference papers of what is currently known about the natural history of oral HPV, what the specific gaps are, what are the clinical significance of these gaps, and how your paper will be addressing this gap.

R: Thank you. We agree that more background information on current knowledge of oral HPV infection may be useful, and we have now added this to the Introduction (page 5, lines 84-94).

C: Minor essential revisions
1) Limitation should include a discussion regarding possibility of sampling error with oral rinse sampling. A recent paper was published in JCM showing that oral rinse sampling may be missing HPV detections (http://jcm.asm.org/content/early/2014/04/03/JCM.00286-14). This would impact on the reliability of repeated sampling over time, i.e. could the incidence/clearance rate be simply a reflection of missed infections due to the sampling methodology?

R: We have now included the limitation of the sampling method to the Discussion (page 12, lines 258-263). We agree that it might have had an impact on the accuracy of incidence and clearance rates. However, we think that this potential error does not affect the difference in the incidence or clearance rates between risk groups because the error should be similar for each group.
2) Limitation should also discuss about the difference between DNA detection (not necessarily an infection) vs. RNA detection (more indicative of an infection). This potentially could explain your finding that there was higher likelihood of clearance in those with higher number of recent oral sex partners i.e. what you are detecting is not actual infection per se (RNA detection) but a transient habitation of HPV in the mouth (DNA detection)?

R: Thank you for this suggestion. We included this limitation and explanation as suggested (page 11, lines 237-242).

C: Discussion
1) Line 201-204. Can you please report the actual difference in incidence rates in study reference 11.

R: We changed these lines as suggested (page 11, lines 221-225). As we did not report overall oral high-risk HPV incidence rates, we reported the incidence rates for HPV-16.

2) Line 206 - what sexual behaviors were adjusted for? the term 'Sexual behavior' is too general.

R: We have now made explicit reference to specific sexual variables (page 11, line 227).

Editors comments:
C: The article should revised before considering its suitability for publication. In particular it should be better put into context with the current state of the art on oral HPV infection.

R: We have now summarised what is known about the natural history of oral HPV infection in the Introduction (page 5, lines 84-94), making the case for this study clearer.

On behalf of all co-authors,

Sincerely yours,

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