Author's response to reviews

Title: HIV Associated High-Risk HPV Infection among Nigerian Women

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Version: 2 Date: 16 October 2013

Author's response to reviews: see over
Re: HIV Associated High-Risk HPV Infection among Nigerian Women

We hereby present a revised version of our manuscript titled ‘HIV Associated High-Risk HPV Infection in Nigerian Women’. Below are the reviewers comments, our responses to them are underlined.

Reviewer 1

ABSTRACT

1) The first sentence of the abstract “the incidence of cervical cancer has remained stable in HIV+ women is misleading and an over-simplification”. We only have good data from western countries with high-levels of screening. We know little about what is happening in areas such as Africa where cART is being rolled out far quicker than screening.

The background of the abstract has been changed. It now reads “In developed countries, the incidence of cervical cancer has remained stable in HIV+ women but the prevalence and multiplicity of high risk HPV (hrHPV) infection, a necessary cause of cervical cancer, appears different comparing HIV+ to HIV- women. Little is known about HIV and HPV co-infection in Africa”

2) All HPV infections are more prevalent in HIV+ women, and increase in multiplicity of infection is a consequence, so it does make sense to focus only on multiplicity as a special outcome per se.

Our paper focuses on the prevalence of hrHPV types in the presence of HIV infection. We did not focus on only multiplicity of infection as a special outcome.

3) The second and third sentences of the conclusion are misinterpretations, as there is no information in this paper on the types that cause pre-cancer and cancer. Infact, it is known that the high prevalence of types in women without lesions (even in HIV+ women – see Clifford et al, AIDS, 2006), are not representative of those that cause cancer. This is because certain types, namely 16 and 18 are far more carcinogenic than others. See paper comparing HIV+ and HIV-cancers in Kenya and South Africa, Int J Cancer, first author de Vuyst.

Persistent hrHPV infections have been established as a necessary cause of cervical pre-cancer and cancer. Our conclusions are based on the prevalent hrHPV types in the study population.

BACKGROUND

4) I am not aware of any literature criticising the IARC classification of high-risk types, and certainly not the cited paper.

5) There quite a lot of data published from Africa on HPV types in HIV+ women. The meta-analysis Clifford et al, AIDS, 2006 is a good start, and there have been many more from the region since.

These papers were reviewed and up to 7 were referenced.

6) The claim that cervical cancer incidence is on average higher in Western than Eastern Africa is tenuous. The GLOBOCAN data cited are almost entirely modelled based on very few data from a couple of cancer registries in select countries across the continent. In any case, even if such a difference is true, the hypothesis that this is due to HPV type differences is not answered by this study, that is more a comparison of HIV- versus HIV+. The West versus East Africa issue should be entirely dropped.

Reports from several studies suggest that regional differences in cervical cancer incidence may be due to differences in the prevalence and types of hrHPV between the regions Li, et. al. 2011. Compared to results from East African studies, our findings support the hypothesis that the prevalence and types of hrHPV in West Africa differ and this may explain the different incidence rates of cervical cancer in these populations.

RESULTS
7) The prevalence of HR-type (single or multiple) positive women that were HIV+ and HIV- is purely driven by the study recruitment source. This proportion should be reported the other way round, i.e. the proportion of HIV+ versus HIV- women that were HR HPV pos. These proportions should be reported in Table 2 (see below)

The proportions have been changed. They are now reported according to HIV status as suggested. The proportions are shown in Table 2.

8) In Table 2, overall HPV prevalence and multiple HPV prevalence can be shown. Rather than p values, which do not show the direction of the difference, prevalence ratios with 95% CIs can be shown.

The p-values show the reader that HPV prevalence is different between HIV+ and HIV- women. Prevalence ratios and 95% confidence intervals are shown in Table 3.

To make this table different to Figure 1, prevalences and prevalence ratios for individual types could be shown among HPV-positive women only, as in Clifford et al, AIDS, 2006.

We have taken Clifford et al, AIDS, 2006 into account.

9) As it stands, Figure 1 is somewhat redundant with Table 2 and could be dropped.
Table 2 shows that the statistical relationship of hrHPV by HIV status. Figure 1 helps the reader easily ascertain the most prevalent hrHPV types by HIV status. Many readers find figures more intuitive.

10) Table 3: data are too sparse to show two different models for single and multiple infection, and anyway would not be expected to be different. Hence present one column only for any HR-HPV infection. The meaning of the PRs for the risk factors (age, sexual partners, marital status, education and age at first sexual intercourse) are meaningless unless the reader knows what category is being compared to what.

The models are comparing the risk factors for HPV by HIV categories. HIV negative women are the reference category. A legend has been added to the table to indicate this. The confidence intervals (CI) are presented to help the reader understand the direction of the risk and the effect of the sample size on the effect estimates. Since the effect estimates p-values were significant and the CI did were not too wide across models, the sample size was sufficient to show a difference between the groups compared and the data are not stretched too thin across strata.

11) I am surprised that no HPV35 infections were found in HIV-neg women, as this is a type that is known to be commonly found in HIV-neg women in Africa and Nigeria. The data should be checked for a technical problem.

The data has been checked, none of the HIV- women had HPV35.

DISCUSSION

12) Be clearer about when discussing different HPV types in Africa versus the rest of the world, and when talking about HIV+ versus HIV-ve in Africa. In general, when citing other papers, it is important not to mix HPV type distribution in the general population with that in severe lesions or cancer, which have different meanings, for the reasons explained above.

The discussion has been modified to make this clear.

13) Drop discussion of West versus East Africa, for reasons stated above.

Our results support this hypothesis. However, this is not emphasized in our conclusions.

14) Longitudinal studies of HPV infection are largely impossible due to the requirement to offer treatment and the enormity of the duration and sample size required. Rather, cross-sectional comparisons of HPV type distribution across different lesion grades up to cancer can offer a similar, but more efficient, reply to the question.

Longitudinal studies of HPV infection are difficult to conduct but not impossible. They provide the best evidence to investigate HPV genotype-specific risks for cervical precancer and cancer outcomes.

15) The last sentence about stable cervical cancer rates is not based on evidence – we badly need studies to show what is happening to cancer in HIV+ women in Africa in the cART era. There are some data (e.g. proportions of cervical cancers that are HIV-positive, see papers from Kenya
and South Africa), that suggest an increasing epidemic of cervical cancer as survival is improved with cART.

The sentence on stable cancer rates has been changed. The suggestion on studies examining cancer among HIV+ women in Africa has been included.

**Reviewer 2**

Major changes:
1. Some information on the HIV infected women such as duration of HIV infection, CD4 counts and whether on antiretroviral therapy.

   We did not collect data on CD4 count or antiretroviral therapy because our study was focused on the prevalence of hrHPV genotype. In addition, HIV- participants who do not usually have CD4 or ART data.

2. How many of these women had cervical intraepithelial neoplasia or invasive cervical cancer?

   We did not collect data on cervical intraepithelial neoplasia or invasive cervical cancer because the focus of our study was the prevalence of hrHPV genotype.

Minor changes:
1. In the abstract, the numbers of HIV positive and negative women seems to be switched.

   This error has been corrected. There should be consistency in comparing HIV positive women to HIV negative women and not vice versa.

   The manuscript has been checked thoroughly. All comparisons are HIV+ to HIV-.

2. Reference numbers should be before the full stop.

   This error has been corrected. All the reference numbers are now before the full stop.

3. Aim of the study should be clearly stated.

   The aim of this study has been clearly stated.

4. In the discussion, "women in Thai" should read 'women in Thailand'

   This change has been made, the sentence now reads “women in Thailand”.

5. What type of brush was used to collect the specimen?

   Ayres spatula were used to collect cervical specimen, this information has been added.

6. SAS institute is located in Cary and not Gary.

   This error has been corrected.

7. Were any of the women vaccinated against HPV 16 and 18?

   Vaccination against HPV is not common, so we did not collect this information.
8. Reference category for all variables to be mentioned in Table 3 and also to indicate if variables were categorical or continuous.

Reference variables and variable type are now included in Table 3 legend.

9. Confidence intervals for the prevalence estimates.

Confidence intervals are provided for the prevalence estimates.

Discretionary changes:

1. Reference to studies from Europe and the Indian sub-continent

Reference was made to several studies in Europe and Asia.

2. Comparison to studies on tissues and other methods of HPV detection

Comparison was made to studies with other methods of HPV detection.

3. Comparison to HPV prevalence in men

The paper is focused on hrHPV in women. Comparison data for men in the study population was not available.

We are grateful that our work is being considered for publication in BMC Infectious Diseases.

Yours Sincerely,

Dr. Sally N. Akarolo-Anthony