Author's response to reviews

Title: Cervical cancer screening by visual inspection in Cote d'Ivoire, operational and clinical aspects according to HIV status

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

We are pleased to submit the revised version of the manuscript originally entitled “Challenges in integrating cervical cancer screening with visual inspection methods in HIV care clinics in Côte d’Ivoire”. Our paper reports the results of a cervical cancer screening program based on visual inspection methods conducted in four HIV care clinics of Côte d’Ivoire, as well as in a population of HIV-negative women. Detailed and pertinent comments were received from the reviewers. They allowed us to write a much better paper which hopefully will now be acceptable for publication in your journal. Please find below our answers to the comments received from the reviewers and BMC Public Health editors.

Yours sincerely,

Dr Antoine Jaquet, on behalf of all co-authors

Reviewer 1: Lynette Denny

Title: Challenges in integrating cervical cancer screening with visual inspection methods in HIV care clinics in Côte d’Ivoire

Version: 1 Date: 19 December 2011

Major revisions

Thank you for the opportunity to review this important paper. As the authors correctly point out screening HIV positive women for cervical cancer is an important part of the care of HIV infected women. The study however suffers from a number of limitations which include:

1] It is cross-sectional
We acknowledge that our study was design as a one shot approach and added this information in the ‘Materials and methods’ section (page 4, line 8).

2] The VIA positivity rate of 9% is very low, particularly for a HIV positive group of women - a rate of around 20% is more likely
Indeed, according to prior reports, we were also expecting to measure a rate of positive visual inspection around 20%. However, recent findings from a study independently conducted by JHPIEGO in different HIV clinics in Côte d’Ivoire during the same period reported a rate of 11% of positive VIA in HIV-positive women (Anderson et al, CROI 2011 Boston, [Abstract n°783]), similar to our findings. Issues related to the ‘lower than expected’ frequencies of positive visual inspection have been added in the ‘Discussion’ section (page 10, lines 9 to 25).

3] Because only 123 women who were VI positive (n = 268) underwent histological sampling, the actual performance of VIA in terms of sensitivity, specificity, PPV and NPV cannot be assessed - the detection rate does not give useful information if a policy is to be formulated as this study sheds no light on how VI actually performs and therefore the likely impact on prevention of cervical cancer and its precursors - a number of recent randomised trials (Sankaranarayan et al, Denny et al) have shown very poor performance of VIA in both HIV negative and positive women. While using VIA to establish the awareness and infrastructure for screening is probably
acceptable, using a screening test whose characteristics and true performance are not defined is potentially harmful.

For logistic and financial constraints, we could not afford to perform colposcopy with directed biopsies in all included women. We acknowledge that both VIA and VILI have poor test performance compared to HPV testing. However, available infrastructures in Côte d’Ivoire currently prevent the conduction of cervical screening strategies based on cytology. Additionally, HPV testing adapted to resource-constraint countries is currently not available on the market. Therefore, we believe that the use of VI methods was the most appropriate approach that have at least the advantage of promoting the awareness and building the infrastructure for cervical screening in HIV clinics in Côte d’Ivoire. These comments have been added in the ‘Limitations’ section (page 12, lines 20 to 25 and page 13, lines 1 to 5).

4] What happened to the 6 women identified with cancer - were they offered treatment?
   All women identified with cancer were offered treatment based on surgery (extended hysterectomy). This information has been added in the ‘Results’ section (page 9, lines 2 and 3).

5] Did the trial not offer participants free treatment if lesions were identified (see last line page 8)? Is this not an ethical requirement?
   Free treatment was indeed offered in case of precancerous lesions or invasive cervical cancer. This information has been added in the ‘Methods’ section (page 6, lines 22 and 24).

6] What type of educational material was offered to the women to obviate the LTFU which is considerable in this study?
   To enhance participation to the cervical cancer screening in our targeted population and obviate LTFU, women were orally counseled about the risk of cervical cancer and the potential benefits of an early detection. This information was provided by a dedicated midwife during group sessions on a daily basis in waiting rooms of the HIV clinics or the national center for blood transfusion. Leaflets to sensitize women to cervical cancer and its prevention were also distributed during these sessions. These precisions have been added in the ‘Methods’ section (page 6, lines 16 to 21).

Unfortunately I think this paper needs major revision prior to publication

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have received honoraria from GlaxoSmithKline and Merck to appear on various speaker fora regarding HPV vaccination and have conducted clinical trials funded by both companies. I have no conflict of interest in reviewing this paper.
Reviewer's 2: Michael Chung
Title: Challenges in integrating cervical cancer screening with visual inspection methods in HIV care clinics in Cote d'Ivoire
Version: 1 Date: 13 December 2011

Major Compulsory Revisions
Title and Objective
1) The title of the manuscript is “Challenges in integrating cervical cancer screening with visual inspection methods in HIV care clinics in Cote d'Ivoire” It is not clear that the paper is describing these challenges and that this is a good title.
We acknowledge that our present study focuses on the main outcomes of a cervical screening procedure based on visual inspection methods according to HIV status. Thus we have modified the title of the manuscript to fit more closely the content of the report. The following title “Cervical cancer screening by visual inspection in Côte d'Ivoire, operational and clinical aspects according to HIV status” has been proposed in this revised manuscript (page 1, lines 1 and 2).

2) On page 1: “We sought to identify some of the operational challenges of a cervical cancer screening approach based on VI among women attending HIV care clinics in Abidjan, Côte d'Ivoire.” Did we answer what the operational challenges are? LTFU was addressed but not really much else. Other operational challenges that would merit discussion include financial, human resources, space constraints, flow of patients, and training costs/needs. It is not clear that this is the purpose of the paper so perhaps the terms “operational challenges” needs to be reconsidered.
As mentioned above, we agree that the main part of the present report focuses more on outcomes related to the conduct of cervical cancer screening according to HIV status than operational challenges related to cervical cancer screening. For that reason we have corrected the objective of the study in the ‘introduction’ section (page 4, lines 2 to 4).

3) On page 11: “Providing cervical cancer screening based on VIA and VILI tests in HIV care clinics appears feasible in the urban area of Abidjan.” How are you defining feasible? Cost? It is not clear that this has been answered.
Indeed, the feasibility was not formally addressed, thus we have removed this statement from the ‘Conclusion’ section (page 14, line 2).

LTFU
4) Was the VIA free? Were any incentives given that might have affected LTFU or return to clinic after phone call such as covering transportation costs?
The entire screening procedure was free of charge as well as the treatment in case of positive findings. No incentives were given to women for returning to the medical visit if they missed their first appointment. Precisions related to financial aspects of the screening procedure were added in the ‘Method’ section (page 6, lines 22 to 24).

5) How soon after VIA was a gynecological exam typically offered? Longer time to appointment can be associated with greater LTFU.
After each positive or inconclusive screening test, women were usually addressed to a colposcopic examination on the same week or the week after to reduce LTFU. Precisions have been added in the ‘Method’ section (page 6, lines 11 and 12).
6) How much follow-up time was given before determining participants “finally attended the colposcopic consultation” vs. was defined as LTFU? LTFU is not defined clearly in general and should be strictly interpreted.
We acknowledge a lack of clarity in the definition of LTFU. The LTFU definition was as follows: ‘Women with positive or inconclusive VI examination were systematically addressed on a weekly basis to a medical consultation. If not showing up to this first visit, women were contacted by telephone to schedule another visit. After a maximum of three attempts (one by week), women who did not show-up or who could not be contacted were considered as ‘LTFU’’. This information has been added in the ‘Method’ section, (page 6, lines 13 to 16).

7) How long did one wait before patient was called? Three calls were made over what time period?
As mentioned above, women were systematically called back during the following week if they missed their first medical appointment for colposcopy with a maximum of three attempts (one per week).

Ineligibility for Cryotherapy
8) On page 10: “The higher frequency of extensive lesions in HIV-infected women observed in our study population might directly impact on their risk of being in need for a delayed treatment.” This is not highlighted in the Results section and should be directly noted if it is discussed at length (eg. State prevalence rates).
A more detailed description of clinical reports associated with positive VI finding have been added to the ‘Results’ section (page 9, lines 9 to 14).

9) It seems you are calculating that among VIA positive, 50% have lesions that are not amenable to cryotherapy. Is that correct? This seems very high. Even among HIV-negative women, you found 27% ineligible. This is much greater than found in most other seminal studies on VIA (eg. Lancet, 1999, 353: 869-73). This needs further comment and discussion.
Our study was not initially designed to perform a ‘see-and-treat’ strategy. Thus, we did not formally address the rate of ineligible women referred for a delayed treatment. However, based on clinical reports of midwives who performed the visual inspection, we found a particularly high rate of positive lesions extending into the endocervical canal, especially in HIV-positive women. This condition is usually retained to postpone cryotherapy. Issues related to these findings have been added in the ‘Discussion’ section (page 11, lines 12 to 22).

10) On page 10 “In Zambia, results from a ‘see-and-treat’ program in HIV care clinics reported that 1477 (38.3%) of the 3855 positively screened women in need for a treatment were ineligible for immediate cryotherapy and referred for physician evaluation.” However, it is not clear to me from this paper that those who were ineligible were only among positively screened women. The paper states a ratio that is compared to total number of women screened (16.7%).
Indeed, the present report does not formally use the number of positively screened women as a denominator but the total number of women screened to present the ratio of women referred for a physician evaluation. We made the hypothesis that the great majority of women who were referred for a positive lesion at visual inspection would not be eligible for an immediate cryotherapy. We have removed the
extrapolation ratio of 38.3% and used the ratio initially stated in the paper (16.7%) (page 11, line 19).

11) In general, it is concerning that there is such a high rate of ineligibility detected and this does not seem consistent with most other studies. It is a concerning message from the manuscript.

As stated above, our study was not initially designed to perform a ‘see-and-treat’ strategy. Thus, we did not formally address the rate of ineligible women referred for a delayed treatment. However, previous studies reporting the outcomes of ‘see-and-treat’ programs based on VIA reported important rates of women referred to medical evaluation. This message has been discussed (page 11, lines 12 to 22).

VIA

12) Please comment on whether VIA alone can be considered effective without colposcopy. A high percentage of VIA positive appears to be negative (44%) after colposcopy and this does not even include those negative after biopsy. Is VIA then really helpful?

What was the quality of the VIA in this study compared to other studies?

Despite an adapted initial training of midwives associated with refresher courses during the study period, a high and sustained proportion of positively screened women were considered negative after colposcopic examination and did not undergo directed biopsy. The rate of false positives according to colposcopic results is higher compared to prior accuracy studies conducted by the IARC in Africa and India were 2887 (33%) of the 8848 women with positive VIA were recused for a directed biopsy. These differences probably reflect the wide range in accuracy parameters (Se, Sp, PPV and NPV) of VI related to the subjective, provider-dependent nature of the test as well as differences in the underlying frequency of disease. However, when considering a ‘see-and-treat’ approach based on visual inspection, a significant proportion of positively screened women might be over-treated with cryotherapy. Although the short term safety of cryotherapy performed immediately after VI has been relatively well addressed, the long term safety, especially in HIV-infected women remains to be explored. Issues related to the drawbacks of VI in field condition have been added in the ‘Limitations’ section (page 13, lines 10 to 22).

13) How do the findings of pre-malignant cervical lesions compare to other studies of HIV-positive women in Africa? This merits discussion as it appears to be very low in comparison.

Indeed, according to prior reports, we were expecting to measure a higher rate of positive visual inspection as well as histologically confirmed precancerous lesions in our present study. However, recent findings from a study independently conducted by the JHPIEGO in different HIV clinics in Côte d'Ivoire during the same period reported a rate of 11% of positive VIA in HIV-positive women [Anderson et al, CROI 2011 Boston, abstract N°783]. Issues related to the ‘lower than expected’ frequencies of positive visual inspection and precancerous lesions have been added in the ‘Discussion’ section (page 10, lines 9 to 25).

Minor Essential Revisions
14) On page 1: “An association between ICC and HIV infection has been reported in sub-Saharan Africa although its strength was weaker than in previous reports from resource-replete settings [2].” is a confusing sentence. 
For a better understanding, the sentence has been rephrased as follows: ‘In sub-Saharan Africa, a significant association between HIV infection and ICC has been reported, although it has been much less strong compared to previous reports from resource-replete settings’ (page 3, lines 5 to 7).

15) On page 1: “In high-resource countries, cytology-based cervical screening has curbed down the incidence of cervical cancer for decades [5].” Just “curbed” and delete “down”. 
The word “down” has been deleted (page 3, line 14).

Discretionary Revisions

16) Why were 3% excluded among HIV-positive and 6% among HIV-negative? Was this difference significant? 
Women excluded from the study presented with exclusion criteria defined in the ‘method’ section (i.e. history of cervical cancer or total hysterectomy, aged <25 or >65 years, pregnancy >20 weeks). The 3.0% of HIV-positive women excluded was significantly lower from the 6.3% of HIV-negative excluded (p <10^{-4}). Among excluded women, 89% of HIV-negative women were excluded for an age>25 years compared to 65% in HIV-positive women (p <10^{-3}). These precisions have been added in the ‘Results’ section (page 7, lines 15 to 18).

17) On page 7: “The 2,998 HIV-positive women had a median CD4 count of 291 [inter-quartile range (IQR) 156-461] cells/mm^3 at enrolment in HIV care and 452 [IQR 301-621] cells/mm^3 at most recent measurements.” How recent were the recent measurements? Within what time period of the VIA? One, two, or three months? 
By ‘most recent measurement’ we meant CD4 count measure at last known follow-up visit for HIV-infection’. The median time between cervical screening and last known CD4 count measure was 4 months [IQR 2-6]. This information has been added in ‘Results’ section (page 8, lines 2 to 4).

18) Do we have a sense of how many women refused VIA that was offered? 
Yes, only six HIV-positive women and two HIV-negative women did not give their consent to participate in the present study. This has been included in the ‘Results’ section (page 7, lines 18 and 19).

19) On page 4 “Due to financial constraints, three of the six adult IeDEA centers in Abidjan, two nongovernmental organizations (ACONDA-CePReF, ACONDAMTCT) and the national center for blood transfusion (CNTS) were selected according to their location in the districts of Abidjan. We randomly selected three sites among the six sites in order to cover all the three districts were IeDEA West Africa sites were implemented in Abidjan (1/1 in Yopougon, 1/1 in Abobo and 1/4 in Treichville).” This is confusing. Were sites selected randomly or based on financial constraints? 
Due to logistic and financial constraints, only three of the six adult HIV clinics involved in the IeDEA collaboration were invited to participate. Two nongovernmental organizations, the ACONDA-CePReF (Yopougon), the ACONDA-MTCT plus (Abobo) and the national center for blood transfusion (CNTS) (Treichville) were selected in
order to cover all the three districts where the leDEA West Africa sites are already implemented in Abidjan. The CNTS was also selected for its capacity to recruit HIV-negative women. We apologize for this confusing sentences that have been rephrased (page 4, lines 11 to 17).

20) Were study nurses and doctors blinded to HIV status?
No, this procedure could not be proposed as HIV-positive women were recruited in HIV clinics and HIV-negative women in the national center of blood transfusion. A sentence has been added in the ‘Method’ section (page 5, lines 1 and 2).

Level of interest: An article whose findings are important to those with closely Related research interests

Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.
Editors comments:

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