PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study
AUTHORS	Mchome, Bariki; Swai, Patricia; Wu, Chunsen; Katanga, Johnson; Kahes; Linde, Ditte Søndergaard

VERSION 1 – REVIEW

REVIEWER	Joel Fokom Dopmgue Department of Gynecology and Obstetrics, Faculty of Medicine and Biomedical Sciences, University of Yaounde, Cameroon.
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	Dear Authors, thank you for the opportunity to review your manuscript entitled “Cohort Profile: The comprehensive cervical cancer prevention in Tanzania”. This is a niece piece of work aimed at assessing the natural history of HPV and cervical cancer in an HIV epidemic population in Tanzania, Eastern Africa. This paper could be improved by addressing the following concerns. In the introduction section of the manuscript, the authors state that the use of VIA as standard screening method contributes to the high burden of cervical cancer in the region. However, it is not clear how the use of a screening test with a low sensitivity can play such role. Indeed, the sensitivity of cytology (Pap test) that has been successfully used for many decades in high income countries is not that high, and may even compare to that of VIA. Please clarify. On the other hand, the introduction is long and could be shortened. In the methods section, it states that data were collected at 14 months interval. Please could authors explain how this interval was chosen? The proportion of HIV positive women recruited in this study seems to be higher than HIV prevalence in the general population. How was this oversampling of HIV positive women achieved? Did you calculate a minimum sample size needed to provide enough statistical power to your results? The plan for statistical analysis is not clearly outlined. Were women who showed up for follow up compensated with transportation fees or some other type of incentives? It is my understanding that the care HPV assay detects 14 HPV types, and not 13. Please verify. The results section seems to be primarily descriptive and not focused, and it is not clear how the authors used the data collected to respond to their study questions. The discussion section is missing, probably because the results section failed to properly display the findings of the study. Although the study enrolment (2nd follow up) is still ongoing, it is worth presenting the preliminary results in such a way that they address at least partially, the study aims. This will allow a

	discussion of the findings that will improve the scientific value to this paper.

REVIEWER	Eileen Dareng Department of Public Health and Primary Care, University of Cambridge, UK
REVIEW RETURNED	01-Apr-2020

GENERAL COMMENTS	This manuscript provides a description of a prospective cohort in Tanzania designed to study the natural history of high-risk HPV infections and to investigate alternatives to cytology for cervical cancer screening in a low- and middle-income country. The authors have provided some results on HPV prevalence. However, there are a few areas of the manuscript that require major revisions to improve the manuscript. Major revisions 1. In the study design, the authors have stated that women were enrolled from cervical cancer screening clinics in three sites in Tanzania. For the majority of the readership who are not familiar with Tanzania, it would be helpful for the authors to provide more contextual information about the country. In particular, information about the source population of the country and how the study population compares to the source population would be helpful for readers to assess generalizability of results from this cohort. 2. It is not clear how the study population was selected. How did women who self-referred to the screening clinics find out about the program, considering the limited awareness of cervical cancer prevention programs in Tanzania? Were these women referred from other hospital departments because they had symptoms suggestive of cervical neoplasia or at high risk. The characteristics of these self-referred participants may be markedly different from the general population. 3. Line 145 – women who were on their menstrual period were excluded. Why? These women are at risk of HPV infection as other women not on their menstrual period and should be screened for cervical cancer after their menstrual period. It is not clear to me why they were completely excluded. 4. There is a lot of ambiguity about the HPV testing algorithm used. Does every participant get three HPV tests – the careHPV, the Hybrid Capture 2 and LiPAExtra? Lines 186 – 193 allude to this, but it is not clear. A more logical approach would be testing using a qualitative test such as careHPV or HC2 and following up with genotyping. The authors should provide some clarification. Secondly, if the qualitative tests are used prior to the genotyping LiPA, then the prevalence of low risk HPV types would be systematically reduced as they would not have been picked up during the qualitative phase of testing. 5. Authors do not report any public involvement in the design or conduct of this study. This is a major flaw of the study design. In the supplementary material (page 8 – publication and dissemination strategy), it is the desire of the authors to involve stakeholders that are crucial to the development of intervention strategies. Community engagement practices and participatory evaluation during study design and conduct are important in engaging stakeholders. 6. In the reporting of results – Table 3 for example, the authors oscillate between hrHPV in the title and HPV in the table itself. The authors need to proofread this manuscript to ensure that they specify hrHPV when they report on findings from careHPV or HC2.

	7. In the description of the cohort in Table 2, the authors have presented results by HIV status, which is understandable considering that the epidemiology of HPV infections is influenced by HIV status. Therefore, it is not clear, why the authors have not been consistent with this in presenting HPV results. Presenting overall hrHPV results in Table 3 without dissecting the prevalence by HIV status is not ideal. Same comment applies for results of cytology presented in lines 264 – 265, and results in the abstracr. 8. The authors have hrHPV results at baseline and follow up, this data is sufficient for more informative results considering the research objectives of this cohort. Based on the work packages described in the supplementary material, it is critical to identify the the prevalence of persistent hrHPV infection, new acquisitions and cleared infections. Therefore, it would be helpful for the authors to provide the prevalence of these hrHPV categories. 9. The future plans for this study are not convincingly clear (lines 301 – 309). How will the cross-sectional data from PROTECT increase power to study persistence, acquisition and clearance. At best, the PROTECT data may be informative in understanding prevalence of disease. Would the authors consider editing this section to be more specific about how the additional studies would be beneficial? 10. Lines 307 – 310. The authors are being very ambitious when they write that they plan to study HPV related diseases using this data. They are limited by the fact that they have data only on hrHPV and not low risk HPV types which would be required to study HPV related diseases such as genital warts for example. Minor revisions • There are some grammatical errors. Authors need another round of proofreading. Examples are on lines 28-30, line 44, line 74, line 75, line 158-160 • The authors overestimate the impact of their work in line 29. This prospective cohort is mainly descriptive – to aid understanding of the distribution and determinants of HPV infection among Tanzanian women. There are several other steps such as treatment, and primary prevention efforts that are required to reduce the burden of disease. • Line 44 – Percentages are not accurate (696/4080 is 17.1%). • Authors should consider including fractions so that it is clear what the denominators for the percentages are and for consistency. For example, in line 45, authors state that 31.6% of participants were HIV positive, it would be more informative to state 31.6% (1289/4080). Same comments for the other percentages in the abstract. • Line 92 – 95: The authors have reported what the most prevalent hrHPV types in the world are. For comparison, they should consider including the HPV types most prevalent in African regions. • Line 121 – The authors refer to “rapid HPV DNA testing” without stating its name. Up till this point in the manuscript, the authors have been referring to careHPV. Please edit for consistency and clarity. • Line 129 – A better term for general would be group specific with a clear definition the first time the term it is used. General could refer to all HPV types. • Line 129 what is statistically adequate number • Lines 160 – 162 - Why was tracing method II used. It doesn’t seem efficient to send an outreach nurse for a home visit only when the necessary samples could be collected at the same time • Line 241 - What fraction of the sample size was achieved?

	• Self-reported CD4 count would be one major source of information bias. Were the CD4 counts verified using health records?

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1
Comment 1: In the introduction section of the manuscript, the authors state that the use of VIA as standard screening method contributes to the high burden of cervical cancer in the region. However, it is not clear how the use of a screening test with a low sensitivity can play such role. Indeed, the sensitivity of cytology (Pap test) that has been successfully used for many decades in high income countries is not that high, and may even compare to that of VIA. Please clarify.

Response #1: Thank you for this valid remark. The test performance of VIA varies depending on the competence of the examiner, and local data have demonstrated that VIA has a very poor performance compared to Pap in a low-income setting like Tanzania. This may results in inability to detect the disease early and provide proper treatment. We have specified this issue further in the manuscript (Line 87-88 in "main document - marked copy").

Comment 2: The introduction is long and could be shortened.

Response #2: Thank you for this suggestion. We have shorten the introduction (e.g. line 88-93, 121-123, 128-129).

Comment 3: In the methods section, it states that data were collected at 14 months interval. Please could authors explain how this interval was chosen?

Response #3: There is no pre-defined optimal duration of time to investigate natural history of HPV and the time interval between two HPV tests, hence, the 14-month follow-up interval was chosen based on several factors. Firstly, Tanzanian guidelines requires that HIV-positive women should be screened yearly, and seeing we have a significant amount of HIV-positive participants, we wanted to ensure that we abided to this as best we could. Secondly, a shorter duration of time may not have been appropriate since most of HPV infections are transient, and whilst a much longer duration time may have been “ideal” from a research perspective, it was outweighed against risk of developing invasive cervical lesions and available resources. Finally, according the project schedule, enrolment was to be finished within the first 14 months, hence, in order to not to put too much strain on the research sites, we planned for the enrolment and follow-up not to overlap. However, enrolment turned out to be much more challenging than expected wherefore we did have an overlap between enrolment and follow-up though without this causing any issues at the research sites. We have now elaborated on our choice for 14-month follow-up in the manuscript (Line 182-186).

Comment 4: The proportion of HIV positive women recruited in this study seems to be higher than HIV prevalence in the general population. How was this oversampling of HIV positive women achieved? Did you calculate a minimum sample size needed to provide enough statistical power to your results?

Response #4: Thank you for this important observation. We agree that this was not clear in the previous version of our manuscript. In order to make sure that we included enough HIV-positive women into the study, we oversampled HIV-positives and conducted a power calculation based on the research group’s previous studies in Tanzania. Previous experience showed that if we recruited 3500 women from screening clinics, approximately 700 would be high-risk HPV-positive and nearly 350 women would be HIV-positive. And if we recruited 500 HIV-positive women from HIV clinics at the

study sites, an estimated 250 women would be HPV-positive. Hence, a total study sample of 4000 women would include an estimated 950 HPV-positive and 850 HIV-positive women. A power calculation was made based on McNemars test in the situation where we compare two diagnostic tests (1: standard test (VIA) vs 2: new test (careHPV)) where the outcome was sensitivity S1 and S2, respectively. Based on our previous studies in Tanzania it was estimated that 180-200 women would have precancerous lesions at baseline (~true positive) when we assumed a significance level of 5% and that the sensitivity of the standard test was S1=30%. We would then with 80% power be able to detect a significant difference if the sensitivity of the new test would be at least S2=44%. As we anticipated that careHPV testing would have a much higher sensitivity, we would have sufficient power in the present study. In the manuscript, we have further specified our sample size calculations and our over-sampling of HIV-positives, which was conducted based on us also enrolling women from the HIV care and treatment clinics at the study sites (Line 171-179).

Comment 5: Were women who showed up for follow up compensated with transportation fees or some other type of incentives? Please verify.

Response #5: Women who attended follow-up as scheduled did not receive any compensation for transport. However, as a surprisingly low number of women attended the follow-up appointment as scheduled, transportation costs were compensated for those women who were reminded to come (by phone or home-visit) as transportation costs is a known barrier for attendance. We have now clarified this in the manuscript (Line 194).

Comment 6: It is my understanding that the care HPV assay detects 14 HPV types, and not 13

Response #6: Thank you for pinpointing this error. We have changed it accordingly (Line 224-225, 244-245).

Comment 7: The results section seems to be primarily descriptive and not focused, and it is not clear how the authors used the data collected to respond to their study questions.

Response #7: Thank you for this remark. As this is a methodological paper with the primary intent to describe how the cohort was established, how it was followed and the demographic profile of the cohort, we have not included the results of the primary objectives of the cohort. A full description of how the cohort was established and the challenges we encountered during follow-up may be a factor to encounter for in the establishment of future African cohort studies, which are rare. The specific objectives of the cohort and their results will be published in separate papers. In the manuscript we have now listed the papers that are already published based on the cohort (Line 144-145).

Comment 8: Although the study enrolment (2nd follow up) is still ongoing, it is worth presenting the preliminary results in such a way that they address at least partially, the study aims. This will allow a discussion of the findings that will improve the scientific value to this paper.

Response #8: Thank you for pinpointing this. The data of second follow-up is still being collected and are yet to be entered into the CONCEPT database, and therefore it is unfortunately not possible for us to add this data to the article. We have now specified in the abstract and in table 1 that the 2nd follow-up is still ongoing (Table 1, Line 56, 341).

REVIEWER 2

Comment 9: In the study design, the authors have stated that women were enrolled from cervical cancer screening clinics in three sites in Tanzania. For the majority of the readership who are not familiar with Tanzania, it would be helpful for the authors to provide more contextual information about the country. In particular, information about the source population of the country and how the study

population compares to the source population would be helpful for readers to assess generalizability of results from this cohort.

Response #9: Thank you for raising this important perspective. We have taken note of this observation and additional information has been provided to describe the setting and source population in more detail (Line 149-157 in "main document - marked copy").

Comment 10: It is not clear how the study population was selected. How did women who self-referred to the screening clinics find out about the program, considering the limited awareness of cervical cancer prevention programs in Tanzania? Were these women referred from other hospital departments because they had symptoms suggestive of cervical neoplasia or at high risk. The characteristics of these self-referred participants may be markedly different from the general population.

Response #10: Thank for this comment. The project was conducted in sites with already established cervical screening services that offer free screening based on the national screening program in Tanzania that was established in 2001. When the project started, awareness raising of the screening services was conducted in churches and mosques close to the study sites, and women attended the screening based on their own awareness of the screening or from the awareness raising. We have provided a more detailed description of which women that were included into the cohort in the manuscript (Line 149-163).

Comment 11: Line 145 – women who were on their menstrual period were excluded. Why? These women are at risk of HPV infection as other women not on their menstrual period and should be screened for cervical cancer after their menstrual period. It is not clear to me why they were completely excluded

Response #11: Thank you for this remark. Tanzania's national cervical screening guideline recommends that women should not be screened while on their periods as it may obscure the vision and impair the VIA interpretation. In order to adhere to the national guidelines, we had to exclude these women if they presented on their periods. However, the women are always encouraged to return after the period is over, and if they did they were included into the project. We agree that this was not clear from our previous description and have outlined this in more detail in the manuscript (Line 165-166).

Comment 12: There is a lot of ambiguity about the HPV testing algorithm used. Does every participant get three HPV tests – the careHPV, the Hybrid Capture 2 and LiPAExtra? Lines 186 – 193 allude to this, but it is not clear. A more logical approach would be testing using a qualitative test such as careHPV or HC2 and following up with genotyping. The authors should provide some clarification. Secondly, if the qualitative tests are used prior to the genotyping LiPA, then the prevalence of low risk HPV types would be systematically reduced as they would not have been picked up during the qualitative phase of testing.

Response #12: Thank you for pinpointing the ambiguity, we agree that the process was not clear in the previous version of our manuscript. As outlined in table 1, the project protocol for sample collection were as follows: Firstly, a vaginal sample was collected with an Aryes spatula for careHPV analysis. Secondly, a vaginal sample was collected with the ThinPrep Pap Test spatula, and finally VIA was conducted. The second sample was firstly shipped to Denmark where it was analysed for cytology after which the remaining material of the samples were sent to Germany and underwent HC2 DNA testing and HPV-positive samples were genotyped using LiPaExtra. Hence, only two vaginal samples were collected. As we had an objective of testing the performance of VIA against Pap, careHPV and HC2 but also wanted to investigate the natural history of HPV, HC2 and Lipa were

required. We have provided an additional statement in the manuscript to clarify this (Table 1, Line 218-219).

Comment 13: Authors do not report any public involvement in the design or conduct of this study. This is a major flaw of the study design. In the supplementary material (page 8 – publication and dissemination strategy), it is the desire of the authors to involve stakeholders that are crucial to the development of intervention strategies. Community engagement practices and participatory evaluation during study design and conduct are important in engaging stakeholders

Response #13: Thank you for this important observation. We acknowledge that it is a flaw in our study that we did not involve the public while designing it. But while conducting the study, religious leaders in the mosques and churches were informed about the study. Further, we will write policy briefs to inform the end users of our results and discuss the public health implication of our findings. We have included this information in the "Patient and public involvement" section (Line 272-276).

Comment 14: In the reporting of results – Table 3 for example, the authors oscillate between hrHPV in the title and HPV in the table itself. The authors need to proofread this manuscript to ensure that they specify hrHPV when they report on findings from careHPV or HC2.

Response #14: Thank you for this advice. We have proof-read the manuscript and changed it according to the suggestion (e.g. line 49, 52, Table 3).

Comment 15: In the description of the cohort in Table 2, the authors have presented results by HIV status, which is understandable considering that the epidemiology of HPV infections is influenced by HIV status. Therefore, it is not clear, why the authors have not been consistent with this in presenting HPV results. Presenting overall hrHPV results in Table 3 without dissecting the prevalence by HIV status is not ideal. Same comment applies for results of cytology presented in lines 264 – 265, and results in the abstract. The authors have hrHPV results at baseline and follow up, this data is sufficient for more informative results considering the research objectives of this cohort. Based on the work packages described in the supplementary material, it is critical to identify the the prevalence of persistent hrHPV infection, new acquisitions and cleared infections. Therefore, it would be helpful for the authors to provide the prevalence of these hrHPV categories.

Response #15: Thank you for these valid remarks, we understand your point of view. However, as HPV acquisition and persistence according to HIV-status is a specific objective of the cohort and is yet to be published in separate papers, we decided not to include these results in the paper but rather focus on the profile of the cohort.

Comment 16: The future plans for this study are not convincingly clear (lines 301 – 309). How will the cross-sectional data from PROTECT increase power to study persistence, acquisition and clearance. At best, the PROTECT data may be informative in understanding prevalence of disease. Would the authors consider editing this section to be more specific about how the additional studies would be beneficial.

Response #16: Thank you very much for the input. We have rephrased the section in order to further clarify our future plans. Specifically, we wish to compare the clinical performance of three potential cervical cancer screening strategies in Tanzania, 1) HC2 testing at varying cut-points of viral load as measured by the RLU value; 2) HC2 testing with VIA triage; and 3) HC2 testing with triage using HPV16/18 genotyping (Line 341-353).

Comment 17: Lines 307 – 310. The authors are being very ambitious when they write that they plan to study HPV related diseases using this data. They are limited by the fact that they have data only on

hrHPV and not low risk HPV types which would be required to study HPV related diseases such as genital warts for example.

Response #17: We agree and have taken note of this and restricted our future plans to only include those that are potentially feasible (Line 341-353).

Comment 18: There are some grammatical errors. Authors need another round of proofreading. Examples are on lines 28-30, line 44, line 74, line 75, line 158-160.

Response #18: Thank you for this observation. We have proof-read the manuscript and addressed the grammatical error in the respective sections as indicated.

Comment 19: The authors overestimate the impact of their work in line 29. This prospective cohort is mainly descriptive – to aid understanding of the distribution and determinants of HPV infection among Tanzanian women. There are several other steps such as treatment, and primary prevention efforts that are required to reduce the burden of disease.

Response #19: We have taken note of this valid remark, and we have changed the manuscript accordingly (Line 30-31).

Comment 20: Line 44 – Percentages are not accurate (696/4080 is 17.1%).

Response #20: Thank you for pinpointing this. The percentage was calculated out of the total number of women who were included in the cohort (696/4043), not the number that was enrolled (4080). We have updated the sentence to clarify this (Line 49).

Comment 21: Line 92-95: The authors have reported what the most prevalent hrHPV types in the world are. For comparison, they should consider including the HPV types most prevalent in African regions.

Response #21:Thank you for this advice. We have now added the specific HPV types that are more prevalent in Africa compared to other parts of the world (Line 104-105).

Comment 22: Line 121 – The authors refer to “rapid HPV DNA testing” without stating its name. Up till this point in the manuscript, the authors have been referring to careHPV. Please edit for consistency and clarity.

Response #22: Thank you for pinpointing this. We have changed the respective sections (e.g. line 41, table 1).

Comment 23: Line 129 – A better term for general would be group specific with a clear definition the first time the term it is used. General could refer to all HPV types.

Response #23: Thank you for this advice. We have changed manuscript accordingly (Line 35).

Comment 24: Lines 160 – 162 - Why was tracing method II used. It doesn’t seem efficient to send an outreach nurse for a home visit only when the necessary samples could be collected at the same time.

Response #24: Thank you for this comment. The follow-up was much more challenging than what we expected, and we believe it is a key finding of this paper that if Tanzania and other low-income countries are to switch to HPV-testing as their primary screening method, the issue of how to ensure

proper follow-up needs to adressed. We chose to have a home-visit reminder for the women who did not attend after receiving a phone call reminder to ensure that as many women as possible attended the follow-up at the clinic, as the self-sampling option (tracing method III) did not allow for VIA and HIV-testing, which are other key elements of the study. However, the 1st follow-up showed that very few women attended the clinic after receiving the home-visit, and therefore we revised our tracing strategy for the 2nd follow-up to only include a phone call reminder and self-sample (Line 194-196).

Comment 25: Line 241 - What fraction of the sample size was achieved?

Response #25: Thank you for this question. Our power calculation stated that we needed a study population of 4000 women (see the answer to comment #4 raised by reviewer 1) and we included 4043, hence, we reached 100% of our desired sample size.

Comment 26: Self-reported CD4 count would be one major source of information bias. Were the CD4 counts verified using health records?

Response #26: We thank you very much for this observation. By mistake this information was not included in the table 1 in the previous version of our manuscript. CD4 counts were traced in the patients' CTC cards and if the information was missing in the card, it was traced in patient files. We have updated table 1 accordingly (Table 1).

VERSION 2 – REVIEW

REVIEWER	Joel Fokom Domgue The University of Texas MD Anderson Cancer Center, USA
REVIEW RETURNED	02-Jun-2020

GENERAL COMMENTS	Dear Authors, Thank you for the opportunity to review the revised version of your manuscript entitled "Cohort Profile: The comprehensive cervical cancer prevention in Tanzania". While some of my concerns have been addressed, there are points that need to be further considered. The authors seem to indicate that this is a methodology paper, and therefore, they have chosen to not present and discuss the results of their study in this report. If this is the case, this should be clarified in the title, and the main objective of this paper highlighted in the abstract and the methods section of the main text. Further, they should explain why they have included some of their initial findings in the present manuscript, to what extent the results presented here contribute to the methodological description of their study, and whether they find it appropriate to present results in a manuscript without commenting on them. In the introduction section of the manuscript, the authors maintain their statement that the use of VIA as standard screening method contributes to the high burden of cervical cancer in the region. Based on a previous report from Tanzania (reference 5), they argue that sensitivity of VIA is very low when performed by unskilled providers with limited supervision. First, the assessment of VIA performance by by Dartell et al, IJC, 2014, relies on cervical cytology, which is not an appropriate reference test to ascertain cervical dysplasia or cancer. In a comprehensive meta-analysis of

	the performance of VIA (with histology of cervical biopsies being the gold standard) in Africa (Fokom-Domgue et al, BMJ, 2015), accuracy of VIA was found to be high in Tanzania. While a limitation of VIA is the subjective nature of the test, as evidenced by its highly variable performance (and the above-mentioned meta-analysis could be referenced here), an advantage of VIA in limited resource settings like in Tanzania is that it can be performed by mid-level providers (even if they are not highly skilled, it is admitted that they can appropriately perform VIA when they are trained). However, the utility of VIA is questioned in limited resource settings when the number of screening rounds per women's lifetime is low, unlike HPV testing for which screening intervals are wider (Please see the following reference: Fokom Domgue and Valea, Journal of Global Oncology, 2018). Therefore, I would suggest that the authors rephrase the introduction accordingly. In the methods section, the calculation of the sample size is based on observed VIA sensitivity. Is it not clear if one of the study objectives is to calculate the performance of VIA, and HPV tests for cervical precancer/cancer detection as part of the CONCEPT study. If so, what will be the reference test (cytology results, or histologically confirmed CIN), and what will be the definition of "true positive" cervical disease? It is my understanding that the sensitivity of 30% for VIA which is referred to here, was calculated using cervical cytology as the reference test. However, it is not clear what was the threshold for the definition of cervical disease (ASCUS, HSIL, or other). Please could you clarify?

REVIEWER	Eileen Dareng University of Cambridge, UK
REVIEW RETURNED	07-Jun-2020

GENERAL COMMENTS	Thank you for taking the time to revise your manuscript to address the comments. Unfortunately, an important concern from my initial review.has not been satisfactorily answered. At the minimum, it would be of interest to readers to know which hrHPV types are present in this population of HIV negative and HIV positive women. It is also not clear how this cohort compares to the source population. Since this women are self referred, the prevalence estimates may not be representative. The authors should consider providing some comparison to population level descriptives from DHS surveys for Tanzania.

VERSION 2 – AUTHOR RESPONSE

REVIEWER 1

Comment #1: The authors seem to indicate that this is a methodology paper, and therefore, they have chosen to not present and discuss the results of their study in this report. If this is the case, this should be clarified in the title, and the main objective of this paper highlighted in the abstract and the methods section of the main text. Further, they should explain why they have included some of their initial findings in the present manuscript, to what extent the results presented here contribute to the methodological description of their study, and whether they find it appropriate to present results in a manuscript without commenting on them.

Response #1: Thank you very much for these remarks. In our abstract, we have now elaborated more on the aim of the paper as well as summarised more of our key findings in the manuscript as also suggested by reviewer#2 (changes in manuscript: ll. 33-34; 296-302). We have not changed the title in order for it adhere for BMJ Open's guidelines for cohort profile articles. In accordance with BMJ Open guidelines for cohort profile articles, we have summarised the most notable results for the cohort so far as well as focused our discussion on lessons learned from the cohort's creation that can be shared to help future researchers: https://bmjopen.bmj.com/pages/authors/ ; https://blogs.bmj.com/bmjopen/2014/08/22/bmj-open-now-publishes-cohort-profiles/.

Comment #2: In the introduction section of the manuscript, the authors maintain their statement that the use of VIA as standard screening method contributes to the high burden of cervical cancer in the region. Based on a previous report from Tanzania (reference 5), they argue that sensitivity of VIA is very low when performed by unskilled providers with limited supervision. First, the assessment of VIA performance by by Dartell et al, IJC, 2014, relies on cervical cytology, which is not an appropriate reference test to ascertain cervical dysplasia or cancer. In a comprehensive meta-analysis of the performance of VIA (with histology of cervical biopsies being the gold standard) in Africa (Fokom-Domgue et al, BMJ, 2015), accuracy of VIA was found to be high in Tanzania. While a limitation of VIA is the subjective nature of the test, as evidenced by its highly variable performance (and the above-mentioned meta-analysis could be referenced here), an advantage of VIA in limited resource settings like in Tanzania is that it can be performed by mid-level providers (even if they are not highly skilled, it is admitted that they can appropriately perform VIA when they are trained). However, the utility of VIA is questioned in limited resource settings when the number of screening rounds per women's lifetime is low, unlike HPV testing for which screening intervals are wider.

Response #2: Thank you for this valid remark. We have rephrased our statement on VIA screening in LMIC according to your suggestions and incorporated the suggested paper as a reference (changes in manuscript: ll.83-87).

Comment #3: In the methods section, the calculation of the sample size is based on observed VIA sensitivity. Is it not clear if one of the study objectives is to calculate the performance of VIA, and HPV tests for cervical precancer/cancer detection as part of the CONCEPT study. If so, what will be the reference test (cytology results, or histologically confirmed CIN), and what will be the definition of "true positive" cervical disease? It is my understanding that the sensitivity of 30% for VIA which is referred to here, was calculated using cervical cytology as the reference test. However, it is not clear what was the threshold for the definition of cervical disease (ASCUS, HSIL, or other). Please could you clarify?

Response #3: Thank you very much for pointing out these issues. It is correct that cervical cytology was the reference test and that threshold was HSIL+ (HSIL, carcinoma in situ and carcinoma). As one of the objectives of the CONCEPT cohort was to determine the test perfomance of careHPV and VIA (line 124) we used cytology results as the gold standard test due to the following reasons: Cytology is a non-invasive screening test that is readily available in Tanzania and easy to perform. We found it would have been unethical to get a histology specimen as part of a routine primary cervical cancer screening for all the women (even the VIA-negative ones). If the women were found to have HSIL+ they were called back in for further investigation based on the national guidelines, in addition to the follow-up appointments that were part of the CONCEPT project. We have elaborated on this in the "methodology" section (changes in manuscript: ll. 160-161).

REVIEWER 2

Comment #4: Thank you for taking the time to revise your manuscript to address the comments.

Unfortunately, an important concern from my initial review has not been satisfactorily answered. At the minimum, it would be of interest to readers to know which hrHPV types are present in this population of HIV-negative and HIV positive women.

Response #4: Thank you for raising this point again. We apologise for not addressing this comment in our previous revision. As part of the results we have now elaborated on the type-specific distribution of HPV in relation to cytology results. Further, we have referenced the paper where these results are published (changes in manuscript: ll. 296-302).

Comment #5: It is also not clear how this cohort compares to the source population. Since this women are self referred, the prevalence estimates may not be representative. The authors should consider providing some comparison to population level descriptives from DHS surveys for Tanzania.

Response #5: Thank you for pointing this out. We have provided data on the HPV distribution among women with abnormal cytology in Tanzania from the HPV data centre and reflected upon how the study population compares to the source population in our discussion (changes in manuscript: ll. 99-103; 334-342).