Author's response to reviews

Title: An Appropriate Interval of Pap Smear Screening Protocol for HIV-Infected Women: A 5.5-Year Retrospective Cohort Study

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Version: 2 Date: 18 October 2010

Author's response to reviews: see over
Reviewer's report

Title: An Appropriate Interval of Pap Smear Screening Protocol for HIV-Infected Women: A 5.5-year Cohort Study

Version: 1  Date: 18 August 2010
Reviewer: Yasmin Adam

Reviewer's report:

Major Compulsory Revisions

1) In the “Results section”; the number of participants’ that were followed up at each Pap smear is not clear. Out of 821 women originally eligible 444 women who had a first Normal Pap smear had repeat Pap smears- and only 15-16% of 821 should have been excluded, this loss to follow-up should be explained.

Response: The number of participants that were followed up at each Pap smear was already self –explanation in the lower part of Fig 1.

Add: especially a number in our study were either ante-partum, or immediate post partum, were required to follow-up at their registered hospitals causing 250 women were lost to follow up by the 6 month visit (36%) and a further 133 (20%) lost at 12 months. This is a loss of over 50% of study participants in the first year of follow-up. An effort to try to establish some relationship between health care providers and HIV- infected women was very difficult because of stigmatization of HIV.

in the Discussion, the last paragraph.

2) What was the follow-up time? This is important. When did the incident abnormality occur? At the first, second, third follow-up Pap smears. What is the median follow-up time? What is the range of follow-up time? It is important to say when the first abnormality after a normal Pap smear was detected as this would indicate when the first follow-up should be. What was the mean/median number of pap smears per patient?

Response: We also already showed the follow-up time and range in the lower part of in Fig 1.

Add: With the median follow-up time of 12 months when the first ASCUS+ was detected. The mean and median number of Pap smears per patient was 2.7 and 2.0, respectively

in the Results, paragraph 4.
3) The authors conclude that 3 and a half years of follow-up is necessary, however with the attrition of patients over time, their conclusions after 2 years cannot be valid.

Response:  We agree.

Add:  If the results are all normal within this particular period of time, these women should then undergo annual cytologic screening.

at the end of Conclusion
in Discussion, paragraph 2

4) In the discussion, paragraph 7 it states that there was only one patient with tissue diagnosis of CIN11-111, and yet there were 19 women with colposcopic diagnosis of CIN 11-111. The fact that they are from a low-socio-economic background and cannot have a biopsy does not make sense. So are these women treated without histological diagnosis? What about the one patient with invasive carcinoma, was this diagnosed by tissue diagnosis?

Response:

Actually we did not take biopsies only 9 patients with ASCUS if they had colposcopic diagnosis of LSILs (HPV/CIN I).
We found only one woman in this group who had colposcopically diagnosed CIN II-III then she had to be confirmed by tissue diagnosis. (As we already mentioned)

Re-write to clarify in the Discussion at the end of paragraph 7

However, 19/24 women who were colposcopically diagnosed CINII-III and/or cytologically diagnosed HSIL were able to undergo loop electrical excision procedure of cervix (LEEP) or cold knife conization at our hospital. There were histologically CIN II-III and invasive squamous cell carcinoma in 63.2% (12/19) and 5.3% (1/19), respectively.
Already mentioned in Results, paragraph 5 and shown in Table 4

5) It is important to bring to the reader that even though the incidence of abnormal lesions is high, these are mainly low grade lesions.

Response:

Add:  Even though the incidence of abnormal lesions was high, these were mainly low grade lesions

in the Discussion, paragraph 8.
Minor Essential Revisions

1. In the Abstract, under methods “associating” should be changed to associated.
2. In the “Methods” section- paragraph 2; the abbreviation VCE should be explained.
3. In the “Methods” section paragraph 2; The current recommendations are that all women who are HIV infected with an ASCUS or more on cytology should be referred to colposcopy, The authors should explain why colposcopy was not offered to all women with an abnormality.
4. In the “methods” section-paragraph 3, one of the variables used is “assumed duration of HIV infection” this should be explained so that the reader understands the robustness of this measure. Similarly “lowest cd4 count” should be explained. Is this the lowest recorded and how many measures did the women have? Is it for eg the lowest of 3, 4 etc measures.
5. Could the researchers have the Pap smears for the one patient with HSIL which turned out to be malignant reviewed?

Response:

1. Change associating to associated

2. Change All Pap smear screenings were performed by gynaecologists using a wooden Ayres spatula and cotton swab with the conventional VCE technique. to All Pap smear specimens were obtained by gynaecologists from the endocervix, cervical transformation zone and discharge at posterior fornix of vagina using a cotton tip stick and Ayre spatula, as described in the VCE technique.

3. Add: According to our policy, colposcopy must be offered in all cases of ASCUS+, but due to the occurrence of lost to follow-up, some of them were not able to have colposcopy.
   in Methods, paragraph 2

4. Add: The assumed duration HIV infection was the duration that was estimated by the patient after counseling and the lowest CD4 count was the lowest CD4 count recorded.
   in Methods, paragraph 3

5. Response: No, as shown in Table 4 and already mentioned in the last paragraph of the Results, 19/24 cases with HSIL were proved by histology (LEEP or conization)

Discretionary Revisions

None

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 declare that I have no competing interests.

Reviewer's report
Title: An Appropriate Interval of Pap Smear Screening Protocol for HIV-Infected Women: A 5.5-year Cohort Study
Version: 1 Date: 26 August 2010
Reviewer: Cynthia Firnhaber
Reviewer's report:
Biomedical Central Infectious Disease Review
24 April 2010
Review of Appropriate Interval of Pap Smear Screening Protocol for HIV-infected Women: A 5.5-year Cohort Study.” Authors Amphan Chalermchookcharoenkit, Chenchit Chayachinda, Manopchai Thamkhantho and Chulaluk komoltri BMC Infectious Diseases Research article

Dear Editor and Team—
This is an important piece of work as information regarding cervical dysplasia from resource limited countries is limited. This article is interesting and demonstrates what we are beginning to understand in these areas. However there are some major revisions needed, which would strengthen and add clarity to the paper before accepting for publication. Please see comments below.

Major Comments

METHODS:
1. What was QA of the NIL baseline pap smear? Was there a second reading or a colposcopy evaluation?
2. How were discrepant results handled between Pap/colposcopy?
3. Was smoking evaluated as standard risk factor cervical dysplasia? Or in this female population, smoking is not part of this culture? If so might state the results or discussion.
4. I need a little clarity of the structure of the study. My understanding is that the patients were educated and consented to the study and were to be followed every 6 months for 5 years. If this is correct then this is a prospective study, not a retrospective study as mentioned in the discussion. The methods section should describe what type of study it is “such as a longitudinal prospective study etc” If however the standard of care for this clinic is to do Pap smears every 6 months and then at 5 years the investigators decided to look back and collect the data done in the clinic retrospectively – then the statement of it being a retrospective study in the discussion is correct. Please add what the study design is in the method section for clarity. I see the first line of the results section states that “STD — medical records of 901 HIV infected women were reviewed to search for results from first Pap smear. (this should be in the methods—this would be consistent with retrospective review)”

Response
1. By our policy, there are no QA for the NIL baseline Pap smear. However, QA was required for abnormality using either the second reader or colposcopy as stated in the methods.
2. It’s already stated at the end of the second paragraph of method by following the guideline of Reference No. 15.

3. **Add:** Smoking was not included in the baseline characteristics because almost all Thai women were not current or ex-smokers.
   
   in Discussion, in the end of paragraph 5

4. It is retrospective study.
   
   **Add:** the STD-medical records of 901 HIV-infected women were reviewed to search for the results from the first Pap smear.
   
   in the Methods, Paragraph 1

   and

   **Add:** Retrospective Cohort Study

   at the end of Title

**RESULTS**

1. Pap smears were done during pregnancy. There has been some articles stating there is a -there is a higher regression rate after delivery. Wondering if this population is an accurate reflection of the general HIV + women. This data is ½ the study N so not sure that this group can be overall – unless title of article states in pregnant and non pregnant HIV women. Did you compare the results between women who were pregnant at baseline and who were not pregnant?

2. How many women became pregnant and then had Pap smears on the study which then regressed (higher rate in pregnancy)? If they were included in the analysis – Wouldn’t this cause some bias in the cumulative incidence in the study?

3. Prevalence of ASCUS+ Please be careful of reporting of the results that women with receiving HAART had higher proportion of cervical dysplasia. This is most likely a reflection that these women had poor immune status and were on ART and also more likely to have cervical dysplasia due to their poor immune status. This relationship is more a reflection of poor immune status. (or it may reflect a possible iris situation but this really would need lots of research to evaluate) This should be explained in full in the discussion as some people could interpret this to mean that ART causes cervical dysplasia.

4. How many women were initiated on ART during the study? What was the change in CD4 during the study and did this impact on cumulative incidence of ASCUS+?

**Response**

1. Although there were baseline Pap smears of 443 women who initially came to the clinic for antenatal care (ANC), but no one became pregnant in the follow-up visit in this study.
   
   **Add:** No one became pregnant included in the follow-up visit in this study.
In Results, paragraph 2

2. The same reason as 1st query.

3. **Add:** This is the most likely reflection that these women had an underlying poor immune status by their own merit without any correlation of HAART.

in Discussion, paragraph 3

4. **Add:** However, we did not look at the change of CD4 count and its impact on cumulative incidence of ASCUS+.

in Discussion, end of paragraph 3

DISCUSSION

1. How do we know that a woman with a baseline negative pap smear then 6 months later has has cytological abnormalities that this represents a false negative of the baseline pap and not a progression of disease? I think we would need some histological evidence that the negative pap was not negative at baseline to make this statement.

2. I am confused by your statement in the second paragraph in the discussion of “The findings prompted us to reconsidered the appropriate interval of Pap smear screenings for HIV infected women by the US Public Health Service....” Do you want to do Paps more often or every 6 month for longer (etc)? What would you changed based on your results?

3. Here the answer to the title should be given or What did you find as an appropriate level of Pap smear screening (refer to statement 2 ) If the team is not able to make a recommendation then the title should be changed to “A retrospective review of cervical disease in HIV + women in Thailand.”

4. Completely agree with you about using CD4 at 350 to start ART for cervical dysplasia—you have nicely demonstrate this. Out of curiosity what were your results when you looked at 200?

5. These women had mean CD4 count of 343 with a CD4 nadir mean of 232. I would not say in the discussion these women were “non-immunocompromised” These patients did have at least mild immunodeficiency. Also mean CD4 in this situation is very deceiving as a few very high or low CD4 (as demonstrated in your range) can really skew the average. Consider using median CD4 in this case might be more reflective of the overall population.

6. I think another significant limitation of this study. Retention in these environments are very difficult and challenging and follow up for Pap smears in most countries is very difficult for all the reasons we are aware of but should be commented on in the discussion especially with such an effort to try to establish some relationship between the clinics and clients as mentioned in the methods. It is very difficult. Also another factor that might have added to the lost to follow up is that half of the patients came from the antenatal clinic and don’t return for a variety of reasons (travel, too much money time off work to get a test for prevention/asymptomatic etc.)
Response

1. By our policy, we can not just use the histological evidence to prove in women with a baseline negative Pap smear.

2. Add: semi-annual Pap smears for at least 3.5 year periods of time should be considered, especially for those women with a baseline CD4 count less than 350 cells/µL. If the results are all normal within this particular period of time, these women should then undergo annual cytologic screening.

in the second paragraph in the discussion

3. Add: Retrospective Cohort Study at the end of Title.

4. Add: result of CD4 count less than 200 cells (37.8% vs. 28.2%)

in result, paragraph 3

Add: result of CD4 count less than 200 cells (37.9% vs.20.9%, p =0.016)

in result, paragraph 4

5. Change mean to median in Results

Add: The median baseline CD4 count was 324 cells/µL (range 2 - 999) and their median CD4 count nadir was 206 cells/µL (range 2 - 930).

in the end of first paragraph

6. Add: An effort to try to establish some relationship between health care providers and HIV- infected women was very difficulty because of stigmatization of HIV.

In Discussion, paragraph 8

Minor comments

Abstract- Background: The first sentence “Cervical cancer is one of the most common AIDS-related malignancies”-- This needs clarification—where? In US/Europe this is not true.

Response Add: in Thailand

BACKGROUND ARTICLE

1. First sentence is a little awkward- would change to something along the lines of “Thailand has an HIV prevalence of 1.5%.”

2. Second paragraph under background please clarify the following sentence: “Our previous study indicated that 13.3% of HIV infected pregnant women had cervical squamous cell abnormalities, while the prevalence of abnormal Pap smears from many studies seemed to be higher (20-40%)” Please clarify if this
20%-40% only in Thailand or worldwide—worldwide some countries can be much higher SA—50% Zambia 76%.

3. Last sentence in the last paragraph is confusing to me. Does this study look at all SIL greater than ASCUS or all SIL including ACSCUS? A suggested sentence to clarify would be “the study includes all the following abnormal pap smears (ASCUS, ASC-H, LSIL, HSIL) designated as ASCUS+.”

Response
1. **Delete**: and has a prevalence of 1.5%
2. Please refer to the Reference 5-8
3. **Change** (atypical squamous cell of undetermined significance or higher grades, ASCUS+)
   To (atypical squamous cell of undetermined significance; ASCUS or higher grades, i.e. atypical squamous cells cannot exclude high grade squamous intraepithelial lesion; ASC-H, low grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; HSIL, squamous cell carcinoma) designated as ASCUS+

**METHODS**
4. Define VCE (not a term used much anymore—haven’t seen this is years)

Response
4. Add: All Pap smear specimens were obtained by gynaecologists from the endocervix, cervical transformation zone and discharge at posterior fornix of vagina using a cotton tip stick and Ayre spatula, as described in the VCE technique in Methods, paragraph 2

**RESULTS**
1. Under cumulative incidence of ASCUS+ section -- the sentence I think should read “There was no statistical difference between development of ASCUS+ from NIL in terms…”
2. In the same section; The last sentence do you mean significant correlations were with ASCUS+ at baseline results or correlation with the cumulative incidence.
3. Any AGUS results?
4. Under Prevalence of ASCUS section—change to Invasive squamous cell carcinoma (CIN 3 is carcinoma in situ)
5. What was the overall pap /colpo correlation rate?
6. Anyway to get information in the patients that “progressed” during the time of the study of the STD rates, condoms used, sexual history (besides at baseline). I know this is very difficult in this setting.

Response
1. **Change** subsequent ASCUS+ and NIL to development ASCUS+ from NIL
2. **Add:** correlation with the cumulative incidence

3. Actually there were no AGUS in our prevalence and cumulative incidence. However, 4 of AGUS after ASCUS+ was found during follow-up

4. **Add:** invasive in Results, the last sentence

5. Please refer to Table 4

6. Sorry, it’s very difficult to conduct the data collection.

**DISCUSSION**

1. Another limitation of the study is lack of viral load but this is very understandable in this setting but should be mentioned.
2. Also would use the term baseline CD4 instead of initial and would use CD4 nadir instead of lowest CD4. Very minor terms changes.
3. Why does the team think there is a stabilization of cumulative incidence after 3.5 years—immunoreconstitution, change of risk factors (wore condoms, stopped smoking??), all those who got disease –got by 3.5 years???

**Response**

1. **Add:** In addition to lack of viral load, in the limitation of study in Discussion

2. **Change** initial CD4 to baseline CD4

3. **Change** the lowest CD4 count to the CD4 count nadir

3. Actually we did not think like you mentioned. However, we lost a highlight sentence

**To more clarify,**

**Add:** semi-annual Pap smears for at least 3.5 year periods of time should be considered, especially for those women with a baseline CD4 count less than 350 cells/µL. If the results are all normal within this particular period of time, these women should then undergo annual cytologic screening.

**in Conclusion**

**FIGURES/TABLES**

1. Very well done overall

Only question In the table2 is Lowest CD4 count P value difference 0.000? Is that a typographical error?

**Respones:** it is correct.

**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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.
Reviewer's report
Title: An Appropriate Interval of Pap Smear Screening Protocol for HIV-Infected Women: A 5.5-year Cohort Study
Version: 1 Date: 25 August 2010
Reviewer: tanvier omar
Reviewer's report:

This is a useful study that adds to the literature on cervical neoplasia and HIV. It is particularly important as most of the research in this field has occurred in developed settings. In order to develop a rational approach to cervical cancer screening, data from resource constraint, high HIV prevalence settings is essential.

Major Compulsory Revisions

1. CONCLUSION:
There is nothing in the findings of this research paper to support the authors’ concluding recommendations for 6 monthly pap smears for 3 years, particularly in a resource constraint setting with competing health needs. Note that even in HIV infected women, with higher rates of persistence and progression, a significant proportion of LSILs will regress over time. LSILs can take up to two years to clear in immune competent women. In all likelihood, this is prolonged in immune-compromised individuals. 6 monthly Pap screening will therefore use valuable screening resources to diagnose the same cervical abnormalities, many of which will resolve over time. The purpose of pap screening is to detect high grade lesions before they become invasive. The documented long duration between LSIL and invasive cancer would further support a wider screening interval. In the context of high grade lesions, 20-30% eventually become invasive over 10-15 years. Even if this lag time is truncated in the HIV setting, it is unlikely to happen within 6 months. Indeed, your study is a case in point. 2852 Paps were performed (on a small number of women) to find 1 invasive cancer in a women with a very low CD 4 count (148) and a 14 year assumed duration of HIV. Those valuable screenings could have served a wider population better. Furthermore, the tapering off of ASCUS+ at 3.5 years is more likely a reflection of a small and exhausted sample rather than being a cut off after which HIV positive women don’t develop cervical lesions.
Advise that these research findings be reported without informing screening intervals as the data does not support the recommendations.

Response: Actually we missed a sentence “If the results are all normal within this particular period of time, these women should then undergo annual cytologic screening”.

Add: If the results are all normal within this particular period of time, these women should then undergo annual cytologic screening.
in Inclusion
2. BACKGROUND: paragraph 2.
One of the suggestions put forward to explain why the authors’ previous prevalence findings could be lower than other published data is the low sensitivity of pap smears. Since the comparison is to other Pap-based screening modalities, this is not a valid reason.
Another suggestion is “different backgrounds”. This needs to be substantiated. Is the prevalence of cervical pre-neoplasia in the Thai general population lower than that of the countries being compared with?

Response: Re-wording to clarify in BACKGROUND, paragraph 2.
Change to However, there are different backgrounds.

3. BACKGROUND: paragraph 2, sentence 3.
It is true that Pap screening suffers from a lack of sensitivity (44-78) %. However, the sentence “even with a NIL…” whilst factually correct is not fair substantiation for this suboptimal sensitivity. A lead time of 3-5 years could result in a significant number of incident cases in this subpopulation. This assertion that the false negative rate explains why 20-30% of women with an initial negative Pap smear will develop a SIL in 3-5 years is repeated in the discussion, paragraph 2. The assumption is thus that the lesions were prevalent at baseline but were missed because of an insensitive test. It completely ignores the possibility that 3-5 years is sufficient time for new SILs to develop.

Response: What I understand is the same as your comment. So re-wording to clarify this sentence by

Change develop to will be later found with

Add: because of an insensitivity test at the end of sentence

4. METHODS:
Were women with ASCUS/LSIL censored at the time of their diagnosis, or re-entered and monitored for persistence, progression and regression? If so, what percentage of them persisted, progressed, or regressed, and over what period? If persistence, progression and regression of ASCUS/LSILs was not measured over the duration of this study, it should be discussed.

Response
Add: All women with subsequent ASCUS/LSIL were not repeatedly enrolled among the rest of the study population.
in the Methods, paragraph 3

5. RESULTS: Paragraph 4; Cumulative incidence of ASCUS+
The authors state that the rate of follow up was low in the last two years. 821 women were enrolled. 15.4% (127odd) had a prevalent ASCUS+ lesion. 694 were NIL. Of these 694, only 444 came back for a second visit. i.e. 250 odd women were lost to follow up by the 6 month visit (36%) and a further 133 (20%)
lost at 12 months. This is a loss of over 50% of study participants in the first year of follow-up. It represents a major limitation, and should be stated as such. Was the data of those who missed a visit or 2 but subsequently returned included in the cumulative incidence arm of the study? If not, please state why not?

Response

Add: especially a number in our study were either ante-partum, or immediately post partum, were required to follow-up at their registered hospitals causing 250 women were lost to follow up by the 6 month visit (36%) and a further 133 (20%) lost at 12 months. This is a loss of over 50% of study participants in the first year of follow-up.

in limitation of this study

Yes, the data of those who missed a visit or 2 but subsequently returned was included in the cumulative incidence arm of the study.

6. DISCUSSION: Paragraph 1.
Part of the explanation for the lower prevalence rate in this study when compared to others is the claim that the majority of women were "non-immune compromised". This is not a fair comment if one considers that the mean CD4 at commencement was < 350, that 29% of participants had CD4 counts <200, and 48% were on HAART at the commencement of this . In fact, could the high number of women on HAART affect the prevalence? Previous studies have shown HAART to reduce SILs. Also, 486 (59.2%) of women were either ante-partum, or immediately post partum. Could this have introduced a sampling bias? This may also explain the large early loss to follow-up, with women having competing demands on their time.

Response:
Add: In addition to different backgrounds, this may be due to the fact that the majority of participants in this study were either ante-partum, or immediate post-partum.

at the end of paragraph 1, in Discussion

7. DISCUSSION: Paragraph 3.
Advise that this paragraph be re-worded in consultation with someone fluent in English.
Response
This paragraph was re-worded as suggestion

Please define, in the methods section, how the assumed duration of HIV was calculated.
Response
**Add:** The assumed duration HIV infection was the duration that was estimated by the patient after counseling.

in the Methods

9. **DISCUSSION:** Paragraph 5.
The assertion that the majority of women were “non-immune compromised” is repeated in this paragraph indicating that this may be the reason HAART had minimal effect. Yet 48% of women were already on HAART at commencement of the study. This needs to be substantiated or reconsidered. The sentence is also somewhat clumsy and may benefit from re-wording.

Response

**Change**  The majority of the participants were non-immunocompromised women, and therefore HAART might have a minimal effect, but was still

**To**  A high number of women were already on HAART at commencement of the study. HAART might have beneficially protective on preventing cervical carcinogenesis

10. **METHODS:**
Please describe in methods, and show the results of multivariate analyses including all variables included in the model. Indicate why a CD4 count of 350 was used to divide CD4 count, or were there more categories used?

Response

**Add:** Multivariated correlation analysis was used to adjust for potential confounding factors.

in the Methods

**Add:** By multivariate correlation analysis, adjusted for the proportion of multipara women and proportion of women with CD4 count < 350 (data not shown), women with CD4 count < 350 cells/µL still had significant correlation with the cumulative incidence of ASCUS+ ($p = 0.043$).

in the Results

Concerning about CD4count<350, currently many institutes including WHO initiate HARRT for all HIV-infected patients who have CD4 count at this level.

**Add:** The CD4 count cut-off point that we used to predict cumulative incidence of ASCUS+ was 350 cells/µL, which is compatible with a study from Brazil[19] and, currently, Thai Ministry of Public Health initiates HARRT for all patients who have CD4 counts at this level.
Minor Essential Revisions

1. Please state in the methods that this is a retrospective review.

Response

Add: the STD-medical records of 901 HIV-infected women were reviewed to search for the results from the first Pap smear in Methods

2. Results paragraph 3 - the text repeats information in table one. Suggest edit text.

Response

Add: most common
Delete: vaginal trichomoniasis, bacterial vaginosis……1.6% …respectively

Discretionary Revisions

1. Title: consider revising title in the light of point number one.

Response

Add: Retrospective Cohort Study at the end of Title

2. It will be useful state the current National cervical screening guidelines in Thailand so that they can be compared to what is being recommended for the subset of HIV infected women.

Response:

Add: Moreover, currently there are no national cervical screening guidelines in Thailand. in Background, at the end of paragraph 3

3. Methods paragraph 3 – adding a subheading of statistical methods should be considered.

Response:

Add: at first Pap smear, and between HIV-infected women with subsequent ASCUS+ and NIL who had a NIL at first Pap smear in Methods paragraph 3

4. Results paragraph 5 – Colposcopic and histological diagnosis of ASCUS+: the last sentence “there were…” would read better if reworded. Consider: Histological assessment confirmed CIN II-III in 12/19 (63%) and squamous carcinoma in 1/19 (5.3%).

Response:

Change as your suggestion
5. DISCUSSION: paragraph 5 – sentence 1 would read better if: -as screening for oncogenic HPV types is a more sensitive predictor of high grade squamous intra-epithelial lesions.

Response:
Change as suggestion

6. DISCUSSION: paragraph 6 – sentence 3: “As a result....” Please clarify that this is Holcamp’s conclusion and not the authors’. Since ASCUS predicts LSIL, it should be managed as for LSIL and does not warrant a colposcopic biopsy.

Response: Yes, this is their conclusion.

Add: they suggested that in paragraph 6 – sentence 3

7. The article will benefit from general grammatical corrections.

Response: This article was firstly edited by an American medical doctor. After revision, this article was edited again for a final approval in grammar

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’