Reviewer's report

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

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Reviewer: Cynthia Firnhaber

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Review of Appropriate Interval of Pap Smear Screening Protocol for HIV-infected Women: A 5.5-year Cohort Study." Authors Amphan Chalermchockcharoenkit, 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)

RESULTS

1. Pap smears were done during pregnancy. There has been some articles stating 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+?

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.)

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.

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—world wide 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+.”

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

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.

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????

FIGURES/TABLES

1. Very well done overall

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

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.