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.

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?

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.

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.

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?

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
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 the study. 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.

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

Please define, in the methods section, how the assumed duration of HIV was calculated.

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.

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?

- Minor Essential Revisions
1. Please state in the methods that this is a retrospective review.
2. Results paragraph 3 - the text repeats information in table one. Suggest edit text.

- Discretionary Revisions
1. Title: consider revising title in the light of point number one.
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.
3. Methods paragraph 3 – adding a subheading of statistical methods should be considered.
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%).

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.

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.

7. The article will benefit from general grammatical corrections.

**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'