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Low grade squamous intraepithelia lesions in HIV-infected women at Chris Hani Baragwanath academic hospital

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Dear Prof Adam

Corrections for final MMed Submission: Dr Portia Kenalemang Manamela

The Examiner's comments are listed below and corrections made are written in **bold**.

List of Corrections

1. Page iii: Paragraph 1 line 3 – punctuation after South Africa is a full stop.
   Line 4 should read… "will therefore"
   Corrected

2. Page x: where is the plagiarism form?
   Form attached as Appendix H

3. Page 1: 2nd paragraph,
   First line should read: "…Both HIV and cervical cancer…" the c in cervical is not capitalised.
   Line 6 should read "…Two observation studies…"
   Corrected

4. Page 1: last paragraph, line 10 should read "…HIV infected women with ASCUS and more severe are…"
   Corrected

5. Page 2: Please see corrections and rephrase line 1 and 2 of the 2nd paragraph
   Rephrased: In South Africa (SA), current data on cervical cancer is lacking. This is due to failure of maintaining the pathology-based cancer registry.

6. Page 2: 2nd paragraph – the words cervical and cancer should not be capitalised as per the corrections.
   Corrected

7. Page 3: see comments regarding 1.3
   2nd paragraph line 2
   Corrected
   HPV is one of the most common sexually transmitted infections in the world.

8. Page 3: last paragraph line 1 should read "…There are more than 40 types that have been…"
   Corrected

9. Page 4: 1st paragraph – insert references for statements on line 9, 11 and 13
   Corrected

10. Page 4: line 12 Bansal et al should be quoted in full with all the names of the authors as per your reference
    (24)

11. Page 4: last paragraph – line 1 – Gaym should include the names of all the authors then et al as per your reference section and it must be accompanied by a reference. The paragraph need rephrasing as well.
    Gaym A, Mashego M and Kharsany A B F et al. showed that LSIL was the most common abnormality identified on Pap smears of HIV positive women. The prevalence of LSIL was 9.2%

and the prevalence of HSIL was 1.3% in this group of women. [24] They also showed that there was a statistically significant association between HIV infection and abnormal Pap findings. They found that abnormal Pap smears occurred in 36% of HIV-positive women as compared to 10.3% of HIV-negative women. [24]

12. Page 4 :last paragraph – line 7 – Omar et al should be quoted with all authors then et al as per your reference section
    Corrected

13. Page 5: last paragraph line 1 – Sankaranarayanan is not in your reference list
    Included in reference list – Ref 22
    Incorrect reference was listed in the reference list. Previous reference 22 removed as it was incorrect and was not used in the final write up.

14. Page 6: 2nd paragraph, line 6 "…using scoring systems like the Reid and Swede scores, colposcopic evaluation can be made more accurate."
    Corrected

15. Page 6: paragraph 3 needs to be rephrased – "The Reid score is a systematic and objective colposcopic method of grading the severity of premalignant cervical lesions."
    Corrected

16. Page 6: 4th paragraph – line 1 – Strander et al must be quoted with all authors then et al. it must also be referenced initially.
    Corrected

17. Page 7: 2nd paragraph – 1.7 should read: Management of cervical pre-cancer lesions.
    Corrected

18. Page 7: 2nd paragraph line 3 should read "… Destructive methods of the TZ include cryotherapy, …while excisional methods include cold knife cone biopsy, …"
    Corrected

19. Page 7: 3rd paragraph line 1 "Colposcopy is not a realiable method for recognising…"
    Corrected

20. Page 7: 4th paragraph – the paragraph is clumsy and needs to be rephrased
    Paragraph rephrased:
    The choice of method for the treatment of CIN is based on the size of the lesion, the age of the patient, HIV status, the patient's desire for future pregnancy and other gynaecological problems.[29,34] Hysterectomy is indicated in women with other gynaecological problems and when future pregnancy is not desired. Ablative methods are useful for women who wish to retain their fertility, but these methods have limitations in that they require histological diagnosis and they cannot be performed in women with a very atrophic cervix and where the lesion involves more than 2 quadrants of the cervix. [36] Other excisional methods like LLETZ and cold knife cone may be used in women who wish to retain their fertility.[36]

    The word gyanaecological should not be capitalised.
    Corrected

21. Page 7: paragraph 5 – the statements made need referencing while the quoted article by Cartier needs full referencing as per your referencing section.
    Corrected

22. Page 8: 1st paragraph 2nd and 14th lines – the quoted article by Kyrgiou needs full referencing as per your referencing section.
    Corrected

23. Page 8: 2nd paragraph 2nd and 11th lines "…the…" should be used and the statement should read "…using the Pap smear…"and"…to be based on the histological specimen…"
    Corrected
    Page 8: 2nd paragraph 11th line is now page 9: paragraph 1 line 6

24. Page 9: 2nd paragraph line 6 should read "…histological evaluation of the entire specimen. This therefore enables a true diagnosis,… or galandular disease. Remove the last statement of paragraph 2.
    Corrected
    Last statement of paragraph 2 removed

25. Page 9:
    The words "cytology" and "colposcopy" should not be capitalised.
    Corrected
    Your statements also need referencing in the text.
    Referencing inserted
    Line 4:
    Corrected: It is however not clear how many of these women with LSIL are just HPV infection or dysplasia. Such information may assist in the management of HIV infected women with a LSIL on their Pap smear and this information will add to our existing knowledge on the subject.

26. Page 12: lines 3, 4 and 5 the word "is" must be replaced by "was".
    Corrected

27. Page 12: figure 2.1. The flow diagram needs to state what happens to HIV neg patients. See comment.
    Flow diagram updated to include that HIV (-) patients with LSIL get a repeat Pap smear if their cervix looks normal. They are then seen at colposcopy if they have recurrent LSIL or HSIL.

28. Page 12: line 7 should read: "On 8th April 2014"
    Corrected

29. Page 13: 2nd paragraph line 2: "…at visit CHBAH were offered an HIV test (personal communication).
    "an" is used before all words starting with "h" – now uniform throughout the write up.

30. Page 13: 4th paragraph, line 2- gynaecologists is not capitalised.
    Corrected

31. Page 14: 2nd paragraph line 2 should read "…informed consent form that allowed their data…"
    Corrected: now on page 15, paragraph 2, line 2.

32. Page 14: 3rd paragraph 1st line: “Ethics approval to do this study was obtained from…”
    Corrected: now on page 15, paragraph 3, line 1.

Chapter 3

33. Page 15: 3rd line – remove the repeated word “findings”
    Corrected

34. Page 15: 2nd paragraph 1st line should read: “Of the 6157 women…”
    Corrected

35. Page 15: 2nd paragraph 3rd line should read: “Of these, 660 women were referred with LSIL. Eight (8) women were excluded from the study as they did not have histology results. The resultant 652 women formed ...”
    Corrected – Now on page 16, 2nd paragraph 3rd line

36. Page 16: 2nd paragraph 4th line should read “…not in their reproductive years or no sexually active.”
    Corrected – now on page 17, 2nd paragraph 4th line

37. Page 18: 1st paragraph line 4 should read “…and the range was between 12 days to a maximum of 212 months.
    Corrected – now on page 19, 1st paragraph line 4

38. Page 21: 1st paragraph line 2 “…was obtained by punch biopsy, Loop excision (of the transformation zone), cold knife cone and hysterectomy…”
    Corrected – now on page 22, 1st paragraph line 2

39. Page 21: paragraph 3 line 2 – remove “under review.” The last paragraph should also have “an histology result…” on both the 1st and 2nd lines.
    Corrected - now on page 22, 3rd paragraph line 2

40. Page 23: last paragraph 4th and 5th lines – “…with CIN3 on histology. This represents a total of …” the word respectively is to be removed. 7th line should read “…colposcopy only had HPV diagnosis on histology.” Use “only” once.
    Corrected – now on page 24, last paragraph 4th and 5th lines
    The last line of page 23 should be part of a new paragraph and be moved as a heading on the next page.
    Corrected – new paragraph now on page page 25

41. Page 24: remove the word “respectively” on both the 2nd line and in the 2nd paragraph, line 4.
    Corrected

42. Page 24: 3rd line should read: 2 on histology, hence 55 women (67.90%) were overdiagnosed.
    Corrected

43. Page 25: the references to your table in the discussions are incorrect.
    References to all tables corrected

44. Page 27: the 1st line should read "The following variables, namely, duration of HIV infection, snuff usage, smoking, parity…" The 6th line should have the word "factors" replaced with infection.
Correections made

45. Please explain and expand on why smoking and snuff was included as variables if too few women's recording of usage was available.
I have gone back to the methods section and stated that cigarette smoking and snuff were only recorded from the year 2010. Smoking is important for progression to cervical cancer and therefore important to report as a variable. I have also stated in the discussion that this is a limitation in our study.

<u>Chapter 4</u>

46. Page 28: use correct punctuation in the 1st paragraph. Use full names of authors as per your references.
Grammar, punctuation and references corrected

The 2nd paragraph, 3rd line – state all quotes with all authors
Corrected

The 2nd paragraph, 3rd line – state all quotes with all authors. The 5th line should read "…Lindeque also found tht about 15-30% of women…"
Corrected

47. The 3rd paragraph 1st line – pleas requote the reference by Omar in full. The 3rd line should read: "In contrast, though, a study done by Saayman F, van Gelderen CJ, Michelow P et al showed that there was no significant increased risk of…"
Corrected

48. What was, if any, in the study from Saayman, the usage of ARVs and could you comment if this could have had an impact on their results
The population used in this study is the same population in Saayman's study. In Saayman's study, antiretroviral treatment use was 41.81% and the use of ART had no effect on the risk of invasive disease or the upgrading of dysplasia.

49. Page 29: your discussion here needs to be reviewed and rephrased in areas. Paragraph 1, 4th line "these women were similar in to the whole study population…" it does not read scientifically and needs to be rephrased.
Sentence was misplaced and therefore removed. Lomalisa's study that showed a difference in the decade is referenced on page 30 in paragraph 1, line 9.

50. Page 29: paragraph 1, line 11 – "JHB hospital" to be written in full as it is not part of your abbreviations.
Corrected

51. Page 29: paragraph 2 does not read correctly and does not make sense.
Paragraph rephrased:
The mean age in our study was 36 years and this is similar to the peak age for development of cervical precursor lesions. The age and parity, in our study, were not associated with a more

severe CIN lesion and this was also a finding in the study done by Omar T, Schwartz S, Hanrahan C et al.[10]

52. Page 30: paragraphs 4 and 5 need to be reviewed, the grammar corrected and the sentences rephrased.
    Paragraph reviewed:
    Intuitively, one would have expected that the progression of CIN would be higher in HIV positive patients and in patients with a longer duration of HIV infection. However, HIV duration was not associated with a statistically significant increased risk of having a more severe cervical lesion. This could possibly be attributed to patients seeking HIV treatment earlier.

53. Page 31: paragraph 1 should read – "Overtreatment can be defined based on either a conservative or a more aggressive approach in the treatment of…"
    Page 31: paragraph 1, line 10 should read "…found to have normal histological results and no SIL."
    Page 31: paragraph 2, line 5 – remove "is" and replace it with "in"
    Page 31: paragraph 3, line 3 – the "C" in cone should not be in capitals.
    Corrected

54. Page 31 needs an extensive review regarding your references from the 4th paragraph onwards as the references do not correlate with your written statements.
    References reviewed and corrected

55. Page 31: 5th paragraph, 3rd line should read "…for the detection of CIN3." There must be a space between CIN and 3.
    Corrected

56. Page 32: paragraphs 1 and 2 need review and rephrasing in an alternate more scientific way.
    Scientific words used and paragraphs rephrased. References also reviewed and corrected.

57. Should read: "A prospective study to determine the common HPV subtypes in our population would be beneficial and will add to our knowledge and understanding of LSIL in HIV positive patients. The knowledge of HPV subtyping may assist in the screening and prediction of patients who will progress to more severe lesions and those who will be at risk of persistence."
    Adjusted

58. Page 34: paragraph 2 and 3 need reviewing and rephrasing with the inclusion of all references.
    Both paragraphs reviewed and rephrased

59. Page 34: paragraph 4 should read - It is important that there is ongoing quality control in colposcopy. Using a uniform scoring system for all colposcopists may reduce the chances of over and under diagnosis, thereby ensuring that patients are properly diagnosed and appropriately treated.
    Corrected

60. Page 35: 2nd paragraph – "The long time interval between the Pap smear and the colposcopy visit…"
    The 6th line should read "Cytology services in the Public Health sector have also not been able to produce reports with results within four weeks. There is a long waiting time for colposcopy."
    Rephrased and Corrected

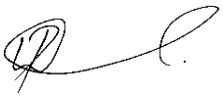
References

61. Number 10: “Schwartz” and not Schwartx
    Number 11: van Gelderen has a non-capitalised v
    Number 19: neoplasia 3: correct spacing between neoplasia and 3
    Number 25: should read Leroy V, not Leroy B. Cervical dysplasia and HIV type 1 and not q.
    Corrected all the above

62. Page 48: Appendix G, Data sheet. “Nurethisterone” should read Nur-Isterate (Nurethisterone enantate)
    Adjusted

End of list of corrections

Yours sincerely



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Dr PK Manamela