Author's response to reviews

Title: Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review

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Author's response to reviews: see over
Dear Editor

BMC Cancer

Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review

We thank you for considering this manuscript for publication in BMC Cancer on the provision that we respond to the referees’ comments. We have taken careful consideration of the constructive comments and suggestions and have modified the manuscript accordingly. We believe we have addressed all the issues raised by the referees as outlined below, and that the changes have significantly improved the manuscript.

We hope that this manuscript will now be suitable for publication.

Yours sincerely,

Dr. Jason Ong
MMed (1st Class Honours), MBBS, FRACGP, PhD (candidate)

Editor Comment 1:

Can you please include a completed PRISMA checklist as an additional file when submitting your revised manuscript. We would also ask that you include a completed copy of the PRISMA flowchart for your study as a figure in your manuscript.

Response: Done. The PRISMA checklist is now included as an additional file. The PRISMA flowchart has now replaced Figure 1 in my manuscript.

Referee 1, Comment 1:
This paper addresses an important tool, DARE, that could help in the early detection of anal cancer in HIV+ MSM. I have one major comment on the hypothesis upon which this study was performed. DARE could be of use for anal carcinoma screening but there seems to be no evidence to advocate it at this moment. The authors have performed a guideline review on the implementation of DARE, which implies the opposite. From a study that looks into the implementation of a screening tool in guidelines one would expect that there is information beforehand that can justify it incorporation in a guideline in the first place. The first question should be, is DARE helpful in the early detection of anal carcinoma. To answer this question one has to screen on original studies and not on guidelines. Although it is stated in the method section that Pubmed and Web of Science were screened for digital examination and anal carcinoma, none of these results have been further elaborated on.

**Response:** The aim of the paper was to show that current advocacy for DARE as an anal cancer screening tool was sparse in guidelines and of those that mentioned it, this was only based on “expert opinion”. We have now elaborated further on our PubMed and Web of Science search in our methods and results section to show the lack of evidence for DARE for anal cancer screening in original studies. Since our submission of the article for review, there has been a recent article by Berry that provided evidence that early detection of anal cancer was possible using DARE. We have included this paper in our discussion.

**Changes made:**

(Page 8, end of 1st paragraph, under Methods)

As a subanalysis, we searched for original articles that utilized DARE alone as a means for anal cancer screening.

(Page 10, last paragraph, under Results)

In our subanalysis of original articles utilizing DARE as a screening tool, we found one article that described the acceptability of DARE to a HIV-positive MSM population[36]. However this study did not provide any efficacy data for DARE.

**Referee 1, Comment 2:**

Some minor essential revisions

p4 last 3 lines: "detecting precursor lesions using an anal cytology-based program with diagnostic high resolution anoscopy to identify anal squamous intra-epithelial lesions (ASIL)”. What is meant here? High resolution anoscopy (HRA) enables histologic based evaluation of mucosal biopsies. This is different from cytology where loose cells obtained via
a brush are evaluated, and as a result the tissue architecture cannot be ascertained. Therefore, ASIL cannot be based solely on cytology results.

Response: We have changed the terminology to HSIL instead to more accurately denote the precursor lesion for anal cancer. A reference is also added to support this terminology. HSIL will be identified using the diagnostic HRA.

Changes made:

(Page 4, Last line, under Background)

2) detecting precursor lesions using an anal cytology-based program with diagnostic high resolution anoscopy (HRA) to identify high-grade squamous intraepithelial lesion (HSIL)[13], which can then be treated using a variety of ablative or other treatments (typically, DARE is also performed in this approach).

Referee 1, Comment 3:

Moreover, anal cytology is used as a pre-screening tool for HRA, but has a low sensitivity in HIV+ MSM (approximately 85% of those screened have abnormal cytograms). As a consequence, most HIV+ MSM require HRA irrespective of the cytology outcome. For this reason anal cytology has been abandoned by most clinicians. I would argue that there are more approaches suggested: anal cytology + HRA, HRA alone and DARE with subsequent cytology/HRA? p5 4th-5th line and 8-9th lines: "anal-cytology based screening”. See my comment above.

Response: We acknowledge the need to describe alternate screening strategies and have now included this in our paper with the relevant references.

Changes made:

(Page 5, 1st paragraph, under Background)

Other potential approaches may include HRA alone[13] or DARE with subsequent cytology/HRA[14]. Some centres have adopted the stance that given the relatively high burden of anal cancer in the HIV population, anal-cytology based screening and treatment for HSIL should be implemented.

(Page 5, 1st paragraph, under Background)

However there remains significant barriers to implement an anal cytological screening service including low sensitivity to detect HSIL due to a large percentage of HIV-positive MSM with abnormal cytology[6], lack of high-resolution anoscopists and no evidence from randomized controlled trials that treatment of HSIL prevents development of anal cancer[16].

Referee 1, Comment 4:
The European AIDS Clinical Society Guidelines are technically speaking not national but supra-national guidelines and should therefore have been excluded based on the followed methodology.

**Response:** This is technically true and given that our methodology searched for both regional and national guidelines (http://hivinsite.ucsf.edu/global?page=cr-00-04#SauguidelineX) we have now adjusted the title of our paper and methodology to reflect more accurately the guidelines that were actually reviewed.

**Changes made:**

(Page 1)

**Title:** Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review

(Page 2, 2nd paragraph, under Abstract)

We systematically reviewed 121 regional and national HIV guidelines and searched for guidelines from http://hivinsite.ucsf.edu/global?page=cr-00-04#SauguidelineX, PubMed and Web of Science databases up to 5th August 2013 for recommendations of DARE as a means of anal cancer screening in HIV positive MSM.

(Page 7, 1st paragraph, under Methods) – deleted the word “national” from the following sentences:

We initially searched for major HIV guidelines through the comprehensive list found on http://hivinsite.ucsf.edu/global?page=cr-00-04#SauguidelineX (accessed 5th August 2013). This website compiles the latest HIV national guidelines from around the world. We searched these 121 HIV guidelines for recommendations regarding the use of DARE for early anal cancer detection.

**Referee 1, Comment 5:**

p14 The conclusions (Anal cancer is an urgent health priority for HIV-positive MSM, and the role of DARE in early diagnosis of anal carcinoma) do not follow from the data aggregated from this study. In my view, the sole conclusions from this study are that there is no evidence for the implementation of regular DARE to prevent progressed anal carcinoma and that therefore it is not mentioned in most guidelines.

**Response:** We have altered our conclusion to reflect the findings of the paper more accurately.
Changes made:

(Page 13, 1st paragraph)

Anal cancer is an urgent health priority for HIV-positive MSMs. Although some experts have recommended regular DARE as a means of detection of anal cancer, few HIV guidelines discuss or recommend DARE as a means of anal cancer screening. There is a need for further studies of the efficacy, acceptability and cost-effectiveness of DARE before its role in anal cancer screening can be determined.

Referee 2, Comment 1:

The authors need to reference and discuss the following paper by Berry that noted that anal cancer may be diagnosed on DARE before symptoms are present. ‘Int J Cancer. 2014 Mar 1;134(5):1147-55. doi: 10.1002/ijc.28431. Epub 2013 Sep 14. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Berry JM1, Jay N, Cranston RD, Darragh TM, Holly EA, Welton ML, Palefsky JM.’

Response: Thank you for this very useful reference. At the time of submission of our paper (Sept 2013), Prof. Berry’s important paper had not yet been published. We have now included this in our discussion.

Changes made:

(Page 11, 1st Paragraph, under Discussion)

A recent study of 138 HIV-positive MSM with anal cancer found that early anal cancer detection was possible in asymptomatic men if they were closely followed up with regular DARE[35]. However, to date, there have not been any studies evaluating whether widespread implementation of regular DARE in those at highest risk for anal cancer (i.e. HIV-positive MSM) would reduce the morbidity and mortality from anal cancer and its management.

Referee 2, Minor comments

Background: P1L2. Remove space after (SCC) and ref to be in compliance with
other references.

**Done.**

P1L5. Remove s from MSMs here and throughout as it is redundant

**Done.**

P1L7. Remove extra space before ‘Anal’

**Done.**

Results: P3L3: Remove ‘any’

**Done.**

Referee 3, Comment 1:

This paper is a literature review of published national guidelines for digital ano-rectal examination among HIV positive MSM. The study contributes to an area with limited literature that is of importance among MSM. There are limited tables synthesizing the results -- while the point that there were few studies recommending DARE is made, the issue of what other countries were recommended (ie no screening) is less clear. More innovative summary / presentation of findings could have improved the impact of this paper.

**Response:** The authors have re-examined how the data may be alternatively presented. We have re-arranged Table 1 and reformatted Table 2 to clearly show the essence of the paper i.e. few guidelines recommend DARE and this is only based on level III (expert opinion) evidence.

**Changes made:**

**Table 1 – Number of HIV guidelines reviewed**

<table>
<thead>
<tr>
<th>Reviewed (number of guidelines)</th>
<th>Not reviewed because was not available in English</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regional</strong></td>
<td></td>
</tr>
<tr>
<td>World (15)</td>
<td></td>
</tr>
<tr>
<td>East Asia and Pacific (1)</td>
<td>Latin America (2)</td>
</tr>
<tr>
<td>Eastern Europe and Central Asia (2)</td>
<td></td>
</tr>
<tr>
<td>Carribean (1)</td>
<td></td>
</tr>
<tr>
<td>South and South East Asia (3)</td>
<td></td>
</tr>
<tr>
<td>Western Europe (3)</td>
<td></td>
</tr>
<tr>
<td><strong>National</strong></td>
<td></td>
</tr>
<tr>
<td>Australia (1)</td>
<td>Argentina (2)</td>
</tr>
<tr>
<td>Botswana (1)</td>
<td>Brazil (6)</td>
</tr>
<tr>
<td>Canada (5)</td>
<td>Bhutan (1)</td>
</tr>
</tbody>
</table>
Table 2 – Guidelines that mention DARE as a means for anal cancer screening

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
<th>Target population</th>
<th>Frequency of DARE</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>European AIDS Clinical Society Guidelines [33]</td>
<td>‘digital rectal exam +/- Papanicolau test’</td>
<td>HIV positive MSM</td>
<td>Every 1-3 years</td>
<td>III (expert opinion)</td>
</tr>
<tr>
<td>US Guideline for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents [38]</td>
<td>‘digital rectal examination as an important procedure to detect masses on palpation that might be anal cancer’</td>
<td>Not specified</td>
<td>Annually</td>
<td>III</td>
</tr>
</tbody>
</table>

For the consideration of the editors, we added the option of figure 2 which essentially summarises visually the data from Table 1. This would be an optional addition if the editor feels it may add value to the paper.

Figure 2 – HIV National guidelines evaluated (in red)
Referee 3, Comment 2:

Minor Essential Revisions.

1. The paper is well written overall although there are places in the discussion that read more like results.

   **Response:** Thank you for noting this. We have now shifted the following paragraph from discussion into results.

   **Changes made:**

   (Page 10, 1st paragraph, under Results)

   We did identify two other guidelines that referred to the issue of anal cancer but did not make specific recommendations about DARE. The British HIV association guidelines for HIV-associated malignancies do not recommend DARE and implies that patients do their own anal examination[32]. The guideline stated that the ‘role of annual anal cytology and anoscopy is not yet proven; however, patients should be encouraged to check and report any lumps noticed in the anal canal’. This again was based only on expert opinion (Level III) with no references to any published studies. It is important to note that these guidelines are currently being revised but in light of the lack of published evidence for DARE, we do not believe that the recommendation is likely to alter at this stage. The World Health Organization’s Treatment and care protocols for the European Region[36] acknowledge that ‘anal cancer is strongly associated with HPV infection and it is significantly more likely among MSM who are HIV infected’ and that ‘any patient suspected of cancer should be examined by an oncologist and referred to the oncology clinic as needed’. However no guidance is provided as to what examination is needed. This again is based only on expert opinion (Level III) with no references to any published studies.