Author's response to reviews

Title: Using population attributable risk to choose HIV prevention strategies in gay men

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Author's response to reviews: see over
RE: 1942917355452732 - Using population attributable risk to choose HIV prevention strategies in gay men

Thank you for the referees’ comments received on the 11th January 2011. Our responses are detailed below in red.

Reviewer 1

Major revision:
1. Overall, the manuscript is clear but the Methods section is missing details which would help the reader considerably in assessing the data and analysis. The authors have cited their previous work but more information is needed. For example, how was circumcision status determined? How was HIV incidence calculated? What method was used to do the multivariate analysis of PAR?
We have included additional information about the PAR method, circumcision status determined, and HIV incidence calculations to the paper.

2. The analysis of HIV infection costs is based on a number of assumptions for which some are based on data. One of the assumptions, the distribution of CD4 counts among treated and untreated people, does not seem to be based on data. Are there data from registries to support the assumption?
We have specified the data sources for all these parameters in the paper.

3. The analysis of costs is also based on the PAR. It seems that it assumes only one behavior at a time drives infection. This is unlikely. Also, if one behavior is reduced or eliminated, then other modes of transmission could take its place. In other words, the cost estimates do not seem to take into account the complexity of behavior.
The PAR represents an estimate of the proportion of infections eliminated, taking account of relationships with other variables.

4. The authors have not included other behaviors which have been shown to be independent predictors of HIV infection among MSM, such as substance use (e.g. see Koblin et al, AIDS 2006 which also has a PAR analysis). We did not include substance use as a category in the model, as drugs used specifically to enhance sexual pleasure, particularly oral erectile dysfunction medications, have been associated with increased sexual risk behaviour, but are not direct risk factors for HIV transmission, and injecting drug
use is not a major risk for HIV transmission in MSM in Australia. We have added this information to the methods.

5. The STIs included are not ulcerative STIs, such as syphilis or HSV-2, which are associated with an increased risk of HIV infection. It is not clear why these were not included. Infectious syphilis and HSV2 was not included in the model, as in the Health in Men (HIM) study the infections were not found to be significantly associated with HIV seroconversions. A statement to this effect has been added to the methods.

6. It is not clear why serostatus of the partner and positioning were analyzed in separate models since positioning is influenced by serostatus of the partner. We were unable to include both sexual position and partner’s serostatus in the same model because of the sparse data which led to empty cells in the combination levels. This information has been added to the methods.

Reviewer 2
Discretionary Revisions:
1. I would suggest a clearer description of the PAR. It is difficult for someone who is not familiar with PAR to fully understand the tables and the analysis. We have included additional information about the PAR method
2. The articles would also benefit from a clearer presentation of why certain risk factors such as “anal warts” and “circumcision” are included in the analysis. Not all readers might be familiar with these aspects of HIV risk taking. Additional information has been added to the introduction
3. In table 1 the person-time (within brackets) is not explained to the reader. For HIV incidence, total person-years were calculated as the time from study entry to the estimated date of seroconversion, or to the end of the study in June 2007 for those who remained HIV-negative. This information has been added to methods. We also have changed person-time to person-years in Table 1.

Reviewer 3
Major Compulsory Revisions
1. The authors should provide a clearer explanation of how to interpret the PAR results for readers unfamiliar with this method, beyond stating that it “controls for confounding among factors.” In Tables 2 and 3, the sums of the PARs for each risk factor are greater than the PARs for all risk factors, presumably because individuals can have more than one risk factor. Please explain how the PAR calculation for an individual risk factor takes into account this phenomenon. In Table 2, for example, 131 of 626 HIV cases are attributable to 10+ casual partners. Does this mean that if all individuals had less than 10 partners, 131 cases would be avoided even though some of those cases were still engaging in
other risk factors? The PAR represents an estimate of the proportion of infections eliminated, taking account of relationships with other variables. This information has been added to the methods and first paragraph of the discussion.

2. The cost calculation is unclear, and it is inadequate because costs are not discounted. Discounting correctly takes account of increasing ARV costs as HIV progresses and delays between infection and entering treatment. If the issues described below cannot be adequately addressed, the authors should consider eliminating the cost results from the paper.

We have undertaken discounting as suggested by the reviewer

3. In the methods section, I was unable to follow the calculation of HIV costs that led to an estimated average health care cost (ARV cost?) per HIV-infected person of $15,553. A table or figure might make this easier to follow.

A new figure has been added describing assumptions of time delays incorporated in costing calculations.

4. In the first sentence only ARV costs are considered, but the second sentence describes “total average costs per person per year” and presents numbers that are substantially lower than the annual costs of ARVs.

The costs analysis has been revised to estimate the average lifetime healthcare costs associated with each HIV infection (over 40 years post infection), factoring the expected delays between infection and clinical care, including initiation of antiretroviral therapy, and discounting all costs to 2010 Australian dollars.

5. The sources of several assumptions are not documented for this calculation, specifically the proportions of HIV-infected on first, second, and third line ART and the proportions of untreated and treated HIV-infected stratified by CD4 cell count. If the sources are estimates, then sensitivity analyses should be considered to reflect the uncertainty around the estimates

We have specified the data sources for all these parameters in the paper.

6. By lumping all costs into the average of $15,553, the authors do not correctly account for the time value of the lag time between infection and diagnosis (see for example citation 20), and between diagnosis and initiation on ARVs. These lag times before initiation on ART need to be accounted for by discounting to present value (Gold et al. recommend an annual discount rate of 3%). In otherwords, avoiding an infection does not immediately save ARV costs because these costs would not have been incurred until ARVs would have been initiated, and a dollar saved today is worth more than a dollar saved in the future.

As describe above, the costs analysis has been revised to estimate the average lifetime healthcare costs associated with each HIV infection (over 40 years post infection), factoring the expected delays between infection and clinical care, including initiation of antiretroviral therapy, and discounting all costs to 2010 Australian dollars.
d. By lumping all costs into the average of $15,553, the authors also ignore the fact that costs become more expensive with time on treatment, as evidenced by the differences in ARV costs between first, second, and third-line that they cite. ARV costs need to be discounted to present value to reflect the fact that higher costs occur in later years. In other words, avoiding a future sequence of first, second, and third-line treatment is not equal to the average cost of ARV treatment for the current HIV-infected population.

We have undertaken discounting as suggested by the reviewer

Minor Essential Revisions

1. In the Conclusion section, the authors state that anal warts are now vaccine preventable. I do not believe any randomized study results have been published about the effectiveness of HPV vaccination in gay men. In addition, because the vaccine is only effective in individuals without prior HPV infection with the relevant sub-types, it is unlikely to be useful for a large majority of adult gay men. The language should be adjusted accordingly. The paragraph has been revised accordingly.

Discretionary revisions

1. Define PAR in the abstract the first time it is used. Done
2. Methods section, STIs: it would be helpful to explain that the associations found by Jin et al. were after adjustment for risk behavior, since anal warts and gonorrhea are obviously associated with risk behavior. Additional information has been added to the introduction and the methods.
3. In the Discussion section the authors state as a limitation that participants in the HIM cohort were not randomly selected. This should be reported more clearly in the methods section in the cohort description, beyond the statement that participants were recruited primarily from community-based sources. The non-random selection of participants has been added to the methods

Yours sincerely

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