Reviewer's report

Title: Long term virological, immunological and mortality outcomes in a cohort of HIV-infected female sex workers treated with highly active antiretroviral therapy in Africa

Version: 2 Date: 30 November 2010

Reviewer: Brian Montague

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Major Compulsory Revisions
1. Need to better delineate the type of sex work in the composition of the cohort and specifically address the discrepancy between the number of sexual partners in their survey (which is low) and prior studies of the high risk group which indicated much high numbers of partners. The presumption is that they have missed the highest risk group in their cohort which, if not the case, needs to be clearly addressed and refuted by the data presented and subsequent discussion.

REPLY 1: As the reviewer remarked, the behavioural characteristics of FSWs described in Table 1 appeared less risky than what had been previously reported from this cohort (ref 12 in the manuscript). Several reasons can explain this discrepancy. Table 1 reports data collected at the time of HAART initiation, not at enrolment in the cohort, which was for nearly all FSWs several months earlier. Meanwhile, cohort participants have been subjected to interventions (promotion of safer sex measures, condom distribution, etc) – so a reported change in sexual behaviour would be expected. Furthermore, women who ended up being on HAART may have modified their behaviour in ways which have not been measured directly in this study. Finally, women may have under-reported their sexual behaviour to staff who have followed them over several months for social desirability reasons. Some of the same factors may also explain the high adherence rate (a combination of the effect of repeated interventions, well-known ‘cohort effect’ selecting towards more compliant populations, and some degree of reporting bias). We have acknowledged the lower risk behaviour of these women in the Discussion (p15). We believe our data are consistent with a 'real life' situation, whereby a HAART programme targeting this population could not stand alone, without any prevention activities. This reduced sexual behaviour after exposure to prevention packages is well documented (including by ourselves, see reference 18 of our paper) ; it is the main source of lower HIV incidence than expected in HIV prevention trials among high-risk populations.
COMMENT: I appreciate the authors thoughtful discussion of the issue above. For the purposes of the article, noting lower risk does not seem sufficient to clarify the issue for the reader who will not have the benefit of reading this elaboration. Since the conclusion is that introducing HAART into a hard to reach and marginalized population is maintainable or sustainable over the long-term, it is important that the paper and the discussion clearly identifies the cohort and critically assesses that issue. The noted collection of risk data at time of HAART initiation rather than at intake into the education and prevention programs seems to be an important limitation of this study that should be addressed.

2. Unless cost-effectiveness and sustainability data is presented, conclusions regarding sustainability need to be dropped as they are not substantiated. All available data in the article suggests that this cohort has received a level of monitoring and intervention that may not be sustainable in most national HIV programs in sub-Saharan Africa without a commitment of additional resources

REPLY 2: Firstly, we think the reviewer may have mis-interpreted 'sustainability' of the approach with 'sustained (virological and immunological) response'. The aim of the paper was to show that HAART in these marginalised populations could achieve a durable effect on biological and clinical outcomes, or that it can be maintained.

This was clearly written in the Title (!), the Introduction section (3rd paragraph – ‘The objectives of the research…’, p6) and the opening paragraph of the Discussion (p13). To achieve our aim required a high level intensity approach. We do not argue in the paper that this is or not sustainable by current programmes, or how it can be transposed to other programmes, although we make the point that investment in this high level quality service is perhaps what is sought by women, and what helps them achieve the desired outcomes. To clarify this meaning we have replace the word 'sustain(ed)' by 'maintain(ed)' in the Discussion(p13, p14, p17). We have also used the word ‘long term effectiveness’ on p16. Secondly, our use of economic terminology (‘economically’, ‘cost-effective’, ‘investments’) was perhaps misleading in a paper that did not intend to measure these outcomes. We have therefore rephrased our conclusion to avoid such confusion (p17).

COMMENT: I am not sure that the substitution of 'maintain' for 'sustain' significantly changes the meaning. The concern is not with the terminology but rather with the conclusions drawn. Essentially the authors conclusion is that with a cohort intervention including high degrees of prevention services, counseling, laboratory monitoring, and resource investment similar to what is provided in more resource plentiful environments HAART can be given with acceptable adherence and immunologic and virologic outcomes that reflect the regular use of medications. That is a very different statement than HAART is an attractive option for use in marginalized populations which reflects a generalization of the
above observation to a context in which the high level of intervention is not feasible or maintainable over the long-term. Is the goal of this paper to advocate for high level investment of resources in these populations? Clearly there is no difference in the biology of these patients so the conclusion that if you get them to take meds they will respond to treatment is neither interesting or novel. The interest and the importance of your valuable study lies in the point that the authors are downplaying, namely what does it take from a systems of care point of view to sustain this level of response. That is what would seem to be most relevant in the discussion and what is missing even with their modifications.

DISCRETIONARY REVISIONS

REPLY 4: We believe that we were careful in this section not to give the impression that we had measured any impact of HAART on transmission (we have not). We simply make the point that current modelling on the use of HAART is only using data from general populations and sero-discordant couples, which may not be generalizable to all situations. There is limited (and conflicting) data that model the possible effect of HAART on transmission among core groups. We argue that in settings where core groups are likely to play an important role in the spread of HIV epidemic, more modelling research is required taking into account empirical data obtained from these groups: this should include data on biological effects (eg. genital shedding) and behavioural ones. We added a word to mention the latter (Discussion p16).

COMMENT: This discussion remains outside of the scope of a cohort intervention study. Modeling studies require outcomes from treatment in the broader population. The very limitations that the authors cite regarding the generalizability of their cohort, the unfeasibility of the interventions for large scale use given the expense, make the data obtained from this sample less relevant for modelling. If the authors can demonstrate that the observations of durable response could be achieved with a sustainable level of resource investment, then the example provided by this cohort would be of great value to modelling the potential impact of increased use of HAART in these communities. Overall, the inclusion of this paragraph raises more questions than it answers.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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