Author’s response to reviews

**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

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**Author’s response to reviews:** see over
12/11/10
Dear Editor
We provide here below a point by point response to the two reviewers comments. We have made changes in track mode in the manuscript and for one figure (Fig 3) – other figures (1,2) are remaining the same
We thank you for the opportunity to revise our work and re-submit and look forward to hearing from you.
Philippe Mayaud (on behalf of co-authors)

Reviewer’s report

Version: 1 Date: 19 September 2010
Reviewer: Brian Montague

Reviewer's report:
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.

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
based on their being a high risk group.

**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).

3. Additional information needs to be presented regarding the statistical methods chosen and the rationale for their use.

**REPLY 3:** We thank the reviewer for his suggestion and we have added this information (p10, last paragraph of Methods).

Discretionary Revisions
4. Unless data on transmission events can be presented, I would suggest deemphasizing the impact on transmission in the discussion since the rate of sexual activity in your cohort is low and you have no data to refute the contention that targeting this group will have minimal impact on the spread of the epidemic.

**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).

5. If transmission risk is to remain a focus of the article, discussion of the patterns of condom use and the differential use between established partners and clients
would be helpful and important.

**REPLY 5**: This is a follow on from the previous point. We do not think the paragraph on p16 warrants any change, and in particular, it should not be lengthened to enter into complex modelling discussion. We hope that our modification at the end of the paragraph cover the nuances expected by the reviewer (see **REPLY 4** above).

**DETAILED COMMENTS**

**DC1. Is the question posed by the authors well defined?**
The article addresses an important question about which there has been limited published data. The primarily delineated goal of the study was to document the outcomes of treatment for HIV amongst a population of sex workers in Burkina Faso. There is however, some lack of clarity with regard to how the information is used in this article and the conclusions to be drawn from it. In the background and in the conclusions, the authors highlight the potential implications for reduction in transmission as a principal motivator for this study.

This offered in theory only as no data is offered in the study regarding transmission events and the only literature they cite states that the epidemiologic impact of targeting these populations would be limited. Secondly, the authors draw the conclusion that long term success in treatment is “sustainable” however we are offered no information regarding the cost of their adherence interventions from which we could make such an assessment. Conclusions of that sort have to be interpreted in the context of a funded cohort and these conclusions may not be generalizable to the large context of HIV care in sub-Saharan Africa.

**REPLY DC1**: We understand the reviewers points and agree with him. We have acknowledged that we have not measured transmission events in this particular population (we would require more complex modelling). We have shown that HAART can achieve durable biological effects in this core group (as it can do in other populations), which are likely to translate into transmission effects. This is of particular importance given the role of core groups in HIV transmission dynamics in some settings like West Africa. We have made clear that this is a theoretical possibility which ought to be investigated more thoroughly.

**DC2. Are the methods appropriate and well described?**
The study is observational with unmatched comparisons between the groups which limits the ability to draw causal inference from the observed correlations. The methods of the adherence intervention and clinical follow-up were well described and appropriate in the context of their cohort. The limitations with regard to virologic monitoring were noted by the authors but significantly reflect typical practices in this region.

Antiretroviral medication use was relatively consistent between the two groups with most all regimens including 2 NRTIs and an NNRTI, again reflecting the standard
practice in the setting. Laboratory monitoring was more frequent than would be
typical outside of a research cohort which may impact the reproducibility and
sustainability of such a program.

**REPLY DC2:** We agree with the reviewer that the level of intervention with this
group was high, and we have acknowledged this in many parts of the paper, but we
argue that it is perhaps necessary to maintain the beneficial biological outcomes.
Our paper does not discuss how to reproduce or ‘sustain’ such a program. We have
avoided this terminology to avoid confusion (see above point 2).

**DC3. Are the data sound?**
With the above limitations, the data presented provide useful and interesting
information regarding the treatment experience in this cohort. The sample sizes are
small limiting the power to distinguish small differences between the groups.
Limited information is given regarding the statistical methods. P-values are
presented for the univariate comparisons without any clear indication in the text or
the table of the method used. The log-rank test was used to assess unadjusted
differences between the survival curves. No tests of difference are offered for the
comparison of the trajectory of CD4 counts and viral loads. The confidence intervals
presented in the graph presumably reflect the uncertainty around the point
measurement without consideration of the information provided by the points prior
and following. While the decision to analyze the data in this fashion may have been
based on the significant component of missing data but this needs to be clearly
discussed. Consideration may be given to whether a repeated measures analysis
would be feasible as a means to improve the power to distinguish differences.

**REPLY DC3:** We thank the reviewer. We have now included a paragraph on
statistical methods. We have added in Figure 3 P-values for the tests of difference
between values (CD4 count [3.A] or % women with detectable PVL [3.B]) at each
time point. After consideration, we have opted not to conduct a repeated measures
analysis and taken the standard approach to monitor response to ART as done in
this literature, in which HAART efficacy is assessed at regular time-point (month 6,
12 and 18 mainly).

**DC4. Does the manuscript adhere to the relevant standards for reporting
and data deposition?** - yes

**DC5. Are the discussion and conclusions well balanced and adequately
supported by the data?**
A notable point, not addressed explicitly in the discussion is the relative lack of
difference in both number of sexual partners and in number of sexual contacts per
week between FSWs and non-FSWs. Given that the authors are questioning the
potential for treatment in this population to impact transmission in the community,
more clarity regarding the population targeted would be important to inform that
discussion. Based on the information, the overall level of sexual activity in all
persons is reported to be low, which may support the argument that targeting this population may be of limited impact epidemiologically. It is difficult to reconcile the reported data regarding partners and activity, median 2 clients, 80% with a steady partner, 2 median sexual acts in the last week. In the prior studies from Burkina Faso looking at categorization of sex work, a range of number partners was noted but for those highly active in sex work (“seaters” and “roamers” much higher numbers of clients were reported (28 and 18 respectively). Does this mean that the cohort failed to get this high risk group into care?

Similarly, in order to really inform a discussion of the sustainability of a treatment intervention in this population, we would need to know more regarding the local care context, the cost and scalability of the interventions used, the intensity of services required to sustain treatment effects (is the intensity highest early on or is intensive case management required over the entire duration on treatment), etc.

What is unique about the FSW population is the social context. If they start on treatment and adhere to treatment, they should have the same immunologic response. The big shortcoming in the discussion as written is the lack of detail regarding this social context and its impact on treatment. Yes, this cohort did relatively well, but what exactly defines this cohort? How can we assess the comparability of this cohort to other cohorts engaged in transactional sex? Have you truly reached the most marginalized amongst them?

**REPLY DCS**

*We addressed the lower than previously reported sexual activity and the issue of whether or not we reached the ‘most marginalised women’ in the response to REPLY 1 above. Similarly, we clarified in REPLY 2 above that the purpose of this study was not directly to provide data on the sustainability of the proposed programme, but to confirm that a good response to HAART can be achieved in the long run among these women. This was clearly written in the Introduction section (3rd paragraph – ‘The objectives of the research...’, p6) and the opening paragraph of the Discussion (p13). What is unique with these women is indeed their poverty (more than the 'average' population), their marginalisation (i.e. very poor access to care), their lack of social (very few good friends because of competition for clients) and their often poor familial support (they very often ran away from their family who ignore all about their 'professional’ activity): all these characteristics - which have been described in our previous publications (e.g. reference 12 of our paper) and cannot therefore be reported in detail here again - can represent a real challenge for proper adherence to daily HAART. We mention this fact in the Introduction (end of 2nd paragraph) and again in the Discussion (p14-15 – ‘Because FSWs often experience...’).

We have now acknowledged that this study population may not be representative of other FSW population (p15, paragraph on limitations), but we persist in the belief that such investment in adherence support is perhaps clearly needed if HAART failures (and their public health consequences in terms of transmission of resistant viral strains) are to be avoided.*
DC6. Are limitations of the work clearly stated?
The authors clearly note the limitations of their study, particularly that it is based in a cohort with free provision of a higher level of care than may be achievable in other care settings and the small numbers of patients limiting the power of the study. Questions remain regarding the potential of selection bias in who was included which is an additional potential limitation not clearly discussed.

*REPLY DC6: we have now mentioned the biases associated with cohort follow-up in Discussion.*

DC7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
This is a new work with appropriate referencing of prior work in the subject area and their relationship to the cohort in which this study is nested.

DC8. Do the title and abstract accurately convey what has been found?
Title accurately conveys the data and observations reported but is discordant with regard to the conclusions drawn.

*REPLY DC8: we have revised the conclusions which are in line with the clinical and biological benefits outcomes that are described in the title.*

DC9. Is the writing acceptable?
With the limitations, the writing is clear and conveys the intended points.
Reviewer's report

Reviewer: Anne Buve

Reviewer's report:

MAJOR COMPULSORY REVISIONS
I have several questions regarding the methods:
1. According to the discussion section the cohorts of the FSW and of the non-FSW were open cohorts (discussion section page 15, second paragraph). This is not very clear from the methods section. Please clarify from when to when women were recruited. I guess there was a limited time period during which the non-FSW were recruited because they were recruited for a trial. What about the FSW: were they also recruited during a limited time period?

REPLY 1: we have now provided a section in the Methodology (p6) clarifying the enrolment periods for the FSW (the period of recruitment for non-FSW was already clearly stated). We have removed the word ‘open’ cohort.

2. I have serious concerns about the losses to follow-up. The authors only took into account loss to follow-up towards the end of the study period (page 9, last paragraph). What about earlier loss to follow-up?

REPLY 2: the losses to follow-up are clearly stated on p11 (Mortality results), 7 women were LTFU. We have now clearly indicated denominators at each visit for the measurement of HIV PBL and CD4 in Figure 3 to see how many women attended and were tested for each outcome a each visit. We hope it provides clarity that there are not losses to follow-up but rather 'missing data’ in the earlier visits (and indeed a smaller number of women made it M36 because of late enrolment).

3. Figure 3 is somewhat difficult to interpret. For instance in figure 3A at 12 months there was a CD4 count for 74% of the FSW and 81% of the non-FSW. It is not clear to me what percentage of the "gap" is due to loss to follow-up and what percentage is due to women being recruited in an open cohort and not yet having reached 18 months of treatment at the end of the study period.
First, I wonder how she arrived at these calculations of 74% and 81% of available CD4 at M12 among FSW and n-FSW respectively.

REPLY 3: As mentioned in REPLY 2 above, we have now clearly indicated denominators at each visit for the measurement of HIV PBL and CD4 in Figure 3 to see how many women attended and were tested for each outcome a each visit. We hope it provides clarity that there are not losses to follow-up but rather ‘missing data’ in the earlier visits (and indeed a smaller number of women made it M36 because of late enrolment).

Results section:
1. Were any data collected on alcohol abuse, a known risk factor for adherence?
REPLY 4: We have now inserted a row on alcohol use in Table 1. This is reported significantly more frequently by FSWs, as now mentioned in Results (p10). We also mention as possible explanation for lower adherence in Discussion (p14).

2. Page 11. I found it striking that among the FSW adherence got better over time (from 83% at 6 months to 100% at 36 months). I would have thought that adherence would get worse. Can the authors please comment on this? I wonder whether there is not an important social desirability bias in these data. This would also put the apparent "discrepancy" between levels of adherence and rates of virlogical failure into perspective.

REPLY 5: As discussed earlier, a social desirability bias cannot be ruled out and could indeed explain the discrepancies in HAART efficacy between the two groups. We have included this element in our revised manuscript. However, the adherence measurement was based on pill count (see3rd paragraph p10), a rather objective indicator, although we concede that 'cheating' might still be possible! While we might have indeed expected a lower adherence over time (as the perceived clinical benefits for the patients tend to fade away), we believe the well maintained (or even better) level of adherence observed in this study came as a result of the persistent efforts and support provided by psychologists, pharmacists and clinicians, who managed to identify (or anticipate) possible causes for sub-optimal adherence and address them in discussion with the study participants. Obviously, this process will take time for its benefits to become apparent.

3. Page 11. The calculation of the overall mortality rate is not very relevant in this case. It would be better to present mortality rate in the first year only, where the highest risk is.

REPLY 6: We already provide the mortality rate at 12 months (Results p11). Adding the mortality rate at 3 years adds only few words (and figure 2). Whilst we agree that the standard result regarding mortality is early up to 12 months, we actually find it useful to show that indeed mortality does not occur much beyond year 1, which in itself validates both the effect of HAART and data on adherence.

MINOR COMMENT
Please correct last sentence of the first paragraph on page 6.

REPLY 7: this was done.