Author's response to reviews

Title: Adherence to antiretroviral therapy during pregnancy and the first year postpartum among women in Ukraine

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Author's response to reviews: see over
Response to reviewers’ comments

Reviewer 1, Marina Giuliano

Reviewer’s report:
This paper addresses the important issue of drug adherence in women in the pre- and post-delivery periods. Some clarifications are needed.

Major compulsory revisions
Methods. Page 5. Lines 101-105. The authors mention participation rates but then there is no information about them in the results section (only a note at the end of the discussion, lines 319-320).
• Thank you, details have been added to the results section – see lines 169-175.

2. Methods. Line 106. The authors state that around one fifth of the women continue ART after delivery and that many of the remainder discontinue it because not meeting the criteria for treatment. Are all the women included in the postnatal survey on ART?
• Yes, only women who continued on ART postnatally were eligible to participate in the postnatal survey on ART adherence. This has been clarified on page 5 line 103.

3. Methods. Lines 109-110. The authors state that characteristics of survey participants were compared with those of women who did not participate but there is no comparison in the results section (Table 2).
• We have added a statement in lines 203-205 to highlight the fact that women participating in the adherence surveys had higher levels of education than those enrolled in the ECS only - the most important difference between the two groups with regards interpretation of the results.

4. Lines 161-162. It is not clear what the denominators refer to.
• There was an error here which has been corrected, and clarification also added to wording (this now appears in lines 170)

5. Lines 163-166. The authors comment here only the antenatal data, but there is no comment on the postnatal data. No statistically significant difference?
• Similar trends were observed in the postnatal group, but the comparisons were not statistically significant due to the smaller sample – details have been added in lines 188-193.

6. Lines 208-210. Lines 217-222. The authors comment on the impact of HIV disclosure. This information should be added to table 4. The same for the information about women unsure of ART effectiveness and the use of ZDVm, not included in Table 4.
• These variables have been added to Table 4, and disclosure of HIV status has also been added to Table 5; corresponding edits to the results section have been made on pages 11 and 12.

7. The authors should also comment in the discussion on the two different measures for adherence that they have used: the CASE tool and the n. of missed pills (differences/similarities in the findings using the two measures).
• A comment on this has been added to the discussion section (lines 392-402)

Minor essential revisions
8. Abstract. Lines 17-18. The authors should modify “self-efficacy” to “ART-related self-efficacy”.
• This change has been made.

Discretionary revisions
9. Introduction. Page 4. Lines 58-63. The two sentences about ART in the general population are not strictly related to the topic of this paper and could be omitted.
• These sentences are directly relevant to the postpartum women who participated in our study; the preceding comment on the WHO Option B policy in Ukraine applies only to women who are currently
pregnant – not to women after delivery, whose access to cART will depend on the availability of cART to adults in the general population (i.e. men and non-pregnant women). We have therefore left these sentences in the introduction.

10. Reference n. 26 is not accessible.
   • The link has been fixed.

Reviewer 2, Anke Reitter

Thank you for this original research work
This manuscript explores the role particular the adherence to ART in HIV-positive pregnant women in Ukraine in the peri- and postpartum period. The authors use survey and self reporting adherence. This is not a new issue, however to have a more local approach about reporting of the experience in the Ukraine might be justified. Adherence has been an important issue in any HIV-infected person, however a special situation occurs in women of childbearing age, here by contrast to the general HIV positive population the adherence is high. This does already reflect the knowledge of reducing MTCT with effective ART. This is the main goal in treatment of HIV-positive pregnant women.
Now the manuscript give information about the type of study (cross sectional) and two “interventions” one at delivery and the second during the first year. You use score systems especially the CASE score system. They conclude to have identified a group of women with a special need for support and counseling to improve the adherence.

1. ART antenatal coverage in pregnancy from 60% to 80% what was the coverage in the study group, especially in the postnatal group, would it be possible to get information about who did not have ART at all? Presumably it was a strict inclusion criteria, even in the postnatal survey?
   • This study on ART adherence was restricted to women who were on ART – for the antenatal survey, women had to have taken ART for at least the last four weeks of pregnancy to be eligible to take part, and for the postnatal study the women had to be currently on ART and between 1 and 12 months postpartum - see clarification line 103. The characteristics of women not receiving ART in pregnancy in Ukraine in the ECS have been described elsewhere (see Bull World Health Organ. 2013;91(7):491-500).

2. Has there been a follow up of the same women taking part in the first survey? Only seven participated in both. It would be much more powered to have the same women for both surveys even than having a smaller number the development postnatally is than studied in a better way, so a comparison between the two important times is lost.
   • Only around a fifth of women continue ART postnatally in Ukraine (see methods line 117), with many of the remainder not yet meeting criteria for treatment. We were interested in the ART adherence of the whole antenatal population (women taking ART for PMTCT only, and with indications for their own health), because this is relevant for future consideration of an Option B+ policy in Ukraine (see line 260). The problem with limiting postnatal survey participation to women who had already participated in the antenatal survey was therefore that we would have needed a much larger antenatal sample to have a sufficient linked sample postnatally (even women continuing on ART postnatally may have chosen not to take part a second time). Increasing the antenatal sample to such a degree was not feasible within the remit of this study, hence the decision to conduct two cross-sectional surveys. We have mentioned the limitations of this study design (line 410) and also added some text to clarify the need for future longitudinal studies to compare adherence during pregnancy and postnatally among the subgroup of women with indications for treatment for their own health (see clarification on line 411-413).

3. The time interval for the second survey: median is 5.3 and the CI 2.4-7.8 months, so the authors should therefore correct the time interval they wanted to look at “the first year after delivery” they have not covered the first year, they have covered the first 6 months.
   • Respondents were eligible to take part in the survey on postnatal adherence if they were between 1 and 12 months postpartum – the median duration between delivery and survey completion was 5.3
months, indicating that half of the respondents completed the survey in the first 5.3 months after delivery, and half completed the survey between 5.3 months and 12 months postpartum. The figures 2.4-7.8 refer to the interquartile range (IQR), not the 95% CI (see Table 1) – thus 25% of the respondents completed the questionnaire more than 7.8 months postpartum, and the responses were well spread throughout the first year after delivery.

4. Only one fifth of all patients continue ART postnatally, this of course will reflect the second survey and reducing the anyway lower numbers further. Here some more baseline information about the second survey would be useful, were women excluded if the ART was discontinued? So the study group for the second survey was really already a “high” risk group due to requiring ART postnatally and therefore a limited answer to the raised question about adherence....
   • See point 1 – postnatal adherence to ART could not be measured among women not on ART postnatally. The postnatal survey group therefore by definition had more severe HIV disease, as they were receiving ART for their own health (rather than for PMTCT only -see description of the difference between antenatal and postnatal survey groups in terms of clinical characteristics – lines 199-202). The statement that patients with indications for treatment were a “high” risk group for poor adherence is not borne out by our data – levels of adherence were similar across the two surveys, and there was no difference in self-reported adherence by HIV disease severity in the antenatal survey (see line 260) while, in the postnatal survey, women with more severe HIV disease were more likely to report complete adherence (line 295).

5. 30% of all patients in Ukraine are enrolled in ECS
   Now the survey was done one a group of patient, the two interventions time could not reliable be chose the compared more complicated and use the database of ECS to find a control group to the study groups, an exclusion criteria was for the study group participants NOT to be included in the ECS data (Table 2)- why?
   Why have the authors chosen to add the ECS data, can they really add anything? Table 2 can mislead
   • Enrolment (or not) in the ECS did not form part of the eligibility criteria for the adherence surveys – a clarification has been added on line 104. For the sub-group of women participating in the adherence surveys who were also enrolled in the ECS, the ECS data provided information on clinical characteristics (e.g. CD4 count and WHO stage) which could not be collected via the self-completed adherence surveys, as shown in Table 2. Headings in Table 2 have now been edited to make it clear that columns 1 and 2 refer to women in the adherence studies AND the ECS, while column 3 refers to women in the ECS only. The rationale for the ECS comparison is to allow for assessment of the representativeness of adherence survey participants.

6. The authors conclude Line 264, page 12“We therefore could not make meaningful comparisons of adherence between the two time periods. “ and yes this is a major criticism of the study, because the aim of the survey and the two time periods which were chosen would be of course to compare the two. Especially the second survey and intervention time is more interesting in terms of adherence as the prenatal period.
   • See comment 2.

7. On page 14, Line 295 “Lower ART-related self-efficacy was related to poorer ART adherence both antenatally and postnatally, and women with a positive depression screening test were also slightly less likely to report complete antenatal adherence.” is a vague conclusion and cannot be supported with the provided data,
   • This sentence has been edited for precision, see lines 365-366.

8. On page 15 , line 325 “Our study design and the use of both WHO Option A and Option B strategies for women requiring ART for PMTCT precluded comparison of adherence during pregnancy and after delivery; ....”
   This is not covered in the presented data, the authors have not given detailed information about option A and B and the study population would be too small to make any conclusion as above quoted...
A definition of option A has been added to the background section (lines 58-60). In line 192, a sentence has been added highlighting the proportion (12%) in the antenatal survey who were on mono/dual therapy, of those with ECS data available (see also Table 2). Results showing the association between receipt of ZDVm and reporting of ≥1 missed dose has been added to Table 4.

9. Table 4 and 5 are not clear both cover factors associated with poor adherence but the authors give the p value for showing significant factors/answers and in one group there were just 25/173 CASE score < 11 available. I feel the p value in Table 4 and 5 should be looked at critical or if at all mentioned just the significant answers highlighted (the factors mentioned as if the pregnancy is planned or not and if the woman lives with a family should be highlighted, that would be sufficient) and is not misleading

- p values ≤0.05 are now indicated in bold in tables 4 and 5.

The authors have given the results of theirs survey in the Ukraine, the adherence has been studied, however there is some weakness in a few issues which I have explained above. The study leaves the reader on top with some disappointment regarding the lost opportunity to compare between the two surveys. The authors have raised some important issues which we should focus on in looking after women with HIV infection in their pregnancies and there is a lot of place for improvement there.