Author's response to reviews

Title: Effect of nutritional supplementation of breastfeeding HIV positive mothers on maternal and child health: findings from a randomized controlled clinical trial

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Author's response to reviews: see over
Responses to the reviewers

Reviewer's report
Title: Effect of nutritional supplementation of breastfeeding HIV positive mothers on maternal and child health: findings from a randomized controlled clinical trial

Version: 1 Date: 10 August 2011

Reviewer: Marzia Lazzerini

Reviewer's report:
The article is very interesting.

Thank you.

The following are all minor essentials revisions.

1. Introduction, first sentence on mean milk production and energy requirements:
I suggest to report a range of values rather than a point estimate (instead than 749 g/day and 626 kCal/day use ranges). Add a reference on international guidelines for nutrition in breastfeeding women, rather than an article.

Thank you, we have added in an international guidelines reference as well as ranges.


2. Introduction, page 4, line 3 to 6 “This can normally be mobilized from their stores at a rate of 172 kcal/day. However mothers with low reserves or diseases with additional metabolic demands like TB or HIV during pregnancy need to compensate by increasing their daily energy consumption.”: this two sentences are unclear. Does it mean that generally mothers do not need an energy supplement , and that only HIV and TB mothers need supplemental energy during BF in developing countries? I suggest to clarify these sentences and to add some more references on the debate on whether ALL breastfeeding mothers need a supplement or not (there are different indications in literature) . I would also mention the level of the food security of the population, their physical activity (most of them are workers and go back to work early) and if this mothers have any access to food supplement during pregnancy. Also, comment on the amount of energy provided by the intervention (280kcal) in comparison with expected energy needs.

Thank you for pointing it out, we can see it wasn’t very clear. We have now amended the paragraph.
3. Introduction, page 4: Add a sentence on expected weight lost during breastfeeding. There is a lot of literature on this, well-nourished women are reported to lose an average of 500-800 g per month for the first six months of breastfeeding (Butte and Hopkinson 1998); under-nourished women are reported to lose, on average, about 100 g per month (Butte and Hopkinson 1998). Also, considered the expected weight lost in comparison with the observed results when commenting the results of the study.

Thank you, we have amended the required paragraphs.

4. Introduction, page 4, line 8: a full point is missing before “we tested….”.

We have added it in.

5. Introduction, page 5 line 5-6 “Mothers whose infants tested HIV negative were counseled on either discontinuing breastfeeding at 6 months, or heat-treating expressed breast milk”: do you mean “infants tested HIV positive (rather than negative)? Or do you mean “tested HIV negative at 6 weeks” or what else?

We meant infants who were asymptomatic and had tested negative at 6 weeks as we didn't do their final bloods till six weeks after cessation of breastfeeding, we have clarified this.

6. Introduction, page 5 line 4-6: I suggest to move these two sentences in the methods sections.

Thank you, we have done so.

7. Methods, page 5: from the registered protocol the supplement is called “Sibusiso ready food supplement”. This may be added also in the article. I also suggest to add a table with the nutritional content of the supplement (or either specify in the text).

Thank you, originally we had thought that mentioning the product might be seen as unethical; however we have now added it in as per your advice. We have also added in a table with the nutritional content of the supplement (Table1)

8. Methods, page 5, last line ”study numbers”: I suggest to modify in “study identification numbers”.

Thank you, we have now amended the sentence.
9. Methods, page 5, regarding randomisation, blinding and contamination/dilution: I suggest to describe these procedures in order, starting from randomisation, then blinding, then dilution/contamination. Also I suggest to move here a couple of sentences that are now of page 7 and 8, and to make explicit who where the outcome assessors. This part could be reordered more or less as follow “Randomisation took place by mothers removing a card pre-marked with group number from a slit in a closed box; this was done to enable them to be confident that the randomisation was unbiased. Randomised was done by a study counsellors who maintained a separate record of the randomisation log. Outcomes were assessed by a separate clinicians (note: verify is this is correct). To ensure that the clinician was blinded, the counsellors issued a brown bag containing either the nutritional supplement or the non-nutritive supplies. Both supplement and the non-nutritive supplies had identical appearance.” The sentences on dilution/contamination could either follow here, or go at the end of the chapter, on page 8. “To prevent dilution of the effect of the intervention and mothers discussing the content of their brown bags, separate clinic visit days were allocated for the two groups. To monitor adherence, a monthly register with mothers’ signatures was maintained as well as a questionnaire was administered to the mothers at every visit discussing daily intake of the supplement and any possible reasons for not taking the supplement including information on any benefits or side-effects that they attributed to the supplement. The counselors also tried to ascertain that the mothers were not sharing the supplement with members of their household.”

Thank you for your suggestions, we have amended the paragraphs as advised.

10. “The counselors also tried to ascertain that the mothers were not sharing the supplement with members of their household.” Add how this was done, if by interview or by direct observation. In the result session, report the results on this point (sharing practices).

This was done by interview. None of them reported sharing of supplement.

11. Methods, page 6, first two sentences “To calculate the sample size, the null hypothesis proposed that the difference between the mean LBM in the breastfeeding control and breastfeeding supplemented groups would be less than or equal to 4 kg. The alternate hypothesis was that the difference would be more than 4 kg”: I suggest to simplify these two sentences in only one sentence, and make clear for the reader (not all are experts in statistics, and the sentence on the null hypothesis may be difficult to read), that the study was designed to detect a difference of > 4kg.

Thank you, we have amended the paragraph.

12. Methods, page 6, line 4, power of the study: why is this 91%? Usually it is
either 80 or 90% Why exactly 91%?

The null hypothesis for the sample size calculations was that the difference between the two groups was \( \leq 4 \) kg. We therefore calculated the sample size using the mean difference and the standard deviations obtained from the population under investigation. The sample size calculated gave us a power of 90.5%.

13. Methods, page 6, line 5 “The true difference between the means was assumed to be 0.00”: Is this correct?

Yes, that’s correct.

14. Methods, page 6, line 6 “The data are drawn from populations with standard deviations of 6.70 and 3.60”: please clarify this sentence.

When piloting the body composition methods in our population, our statistician used the means and standard deviations obtained from the sample to calculate the sample size.

15. Methods, page 7, Karnofsky score: specify for the reader what this score is for.

Thank you for your suggestion, we have added in the details.

16. Methods, page 7 “When indicated they were started on ART”: specify what indication was followed. Specify if that was the WHO recommendations, a local adoption, or else.

We used national recommendations.

17. Methods, page 9 “As low BMI is considered to be an important prognostic marker for breastfeeding HIV positive women.” What is the BMI cut off which proved to have prognostic value? Is your cut-off (BMI< 25) an adequate cut-off, or should you go for a lower cut-off?

The median BMI was around 26, therefore we used < 25 as a cutoff.

18. Results, page 10, line 19: remove a full point after “supplement”

Thank you, we have removed it.
19. Results, on dietary intake: how was the dietary intake, adequate to the needs or not?

We have added in the details.

20. Results, page 11, line 9 “In mothers with BMI # 24.9kg/m2; no significant effect of the supplementation was seen except in LBM where the supplemented group had a significantly lower loss in LBM (0.098kg) compared to the control group” : ..”: substitute the semi-comma with a comma (after “In mothers with BMI # 24.9kg/m2.2). The value of LBM is different from what reported in table 3, what value is it?

This was the value obtained using GEE. The table has the values from the independent T test.

21. Results: add a table with children characteristics at baseline.

We have included this, see table 3.

22. Results: table 1: why some continuous measures are reported as mean and SD, and others as mean and IQR?

Means and standard deviations (SD) are reported for the normally distributed variables and medians with their interquartile ranges (IQR) are reported for the variables with a skewed distribution.

23. In the discussion I suggest to add some comments on the following points:
a) The major finding of the study to me is low acceptability of the food supplement. This is a major finding which well sustains the debate on what types of intervention should be prioritised. Comment with reference on other acceptability studies in other regions.

Thank you, we have included some references.

b) Intensity of the intervention: may it be that calories are not enough to make a difference of 4 kg? Any locally acceptable and cheap food that could be further studied?

That is definitely possible; this is included it in our limitations.
c) Nutritional state of the population. Comment on BMI range of values among mothers. The mean BMI and the IQR are quite high. Was any mother underweight? Any difference in results if a BMI cut-off of 20 is taken instead than 25?

*There were only 2 mothers with a BMI < 20, therefore we would not have been able to analyse appropriately.*

d) Comment on dietary intake in the population (see point 19)

*We have included this information.*

24. Discussion, very last sentence: remove a full point.

*Thank you, we have removed it.*

25. Abbreviations: if the abbreviation list is requested by the journal, add the full list (not only HIV).

Thank you added

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being Published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
'I declare that I have no competing interests'
Reviewer's report
Title: Effect of nutritional supplementation of breastfeeding HIV positive mothers on maternal and child health: findings from a randomized controlled clinical trial

Version: 1 Date: 14 August 2011

Reviewer: Lars Thore Fadnes

Reviewer's report:
The authors ask an important, relevant and well defined question. The methodology is in general good and the analyses well chosen. The data seems to be good, although it is unclear whether they are sufficiently large to answer some of the questions related to the health outcomes of the infants. The choice of references and literature seems to be good. There is a discussion on limitations, although this could benefit on being extended a bit. The article is well written.

Thank you

Major Compulsory Revisions:
1. Has sample size calculations been done also for all the main presented infant health outcomes (growth, diarrhoea and lower respiratory tract infections)? If not, please present post-hoc power calculation with the sample size that was used.

As both groups were breastfed, we wouldn’t expect any difference in terms of opportunistic infections. However, we looked at the WAZ scores using the means and standard deviations obtained at 6 months.

Please see printout from STATA as below:

Sampsi 0.61 0.15, sd1(1.17) sd2(1.13) n1(63)

Estimated power for two-sample comparison of means

Test Ho: m1 = m2, where m1 is the mean in population 1 and m2 is the mean in population 2

Assumptions:
alpha = 0.0500 (two-sided)
m1 = .61
m2 = .15
sd1 = 1.17
sd2 = 1.13
sample size n1 = 63
n2 = 63
n2/n1 = 1.00
Estimated power:

\[ power = 0.6121 \]

2. The nutritional supplement sounds to be rather small in terms of weight and energy content. Please add to the conclusions something indicating the magnitude of the supplementation and also add some discussion on how a larger nutritional supplement could have given different outcomes.

Thank you, we have amended the conclusions.

3. What is the rationale for the opposite directions of the change between the control and interventions groups in LBM and FM (and tendency in BMI)? Might the calculations of FM or LBM be inaccurate?

We used the standard calculations as described (IAEA), they were calculated by two independent observers.

4. The conclusion in the abstract could be worded with more uncertainty as the findings seemed to go in both directions (control vs. intervention). Currently reading: “The nutritional supplement had a limited beneficial effect on preserving the lean body mass of the breastfeeding mothers with a low BMI.” Suggested alternative: “A 50 g daily nutritional supplement to breastfeeding mothers had a no or limited effects on mother and child health outcomes”

Thank you, we have amended the abstract.

Minor Essential Revisions:

5. The following sentence is unclear and needs to be clarified:

“that exclusively breastfeeding mothers require an increased energy intake of 626 kcal/day; this can normally be mobilized from their stores at a rate of 172 kcal/day”

Thank you, we have amended the sentence.

6. Please add something like the following to introduce the Karnofsky score to unfamiliar readers: “to measure well-being and activities of daily life”

Thank you, we have described the Karnofsky score.
7. Please add a short description of the performance threshold Karnofsky score of 80% that was used for categorisation.

Thank you, we have now described it.

8. The following sentence is unclear and needs to be clarified:
“As low BMI is considered to be an important prognostic marker for breastfeeding HIV positive women, all parameters, where possible were analysed according to BMI category”

Thank you, I have clarified the sentence

9. Were the analyses and categorisations pre-defined before the analyses were started? (If not, add this to limitations).

Categorisations for BMI were not pre-defined, I have added this to our limitations.

10. Please move some of the conclusions into the discussion section – particularly where you will need references.

Thank you, I have amended the discussions.

Discretionary Revisions:

11. Results:
Remove one of the double dots: “supplement.”

Thank you, we have amended it.

12. Table 2 and 3:
Instead of indicating “P value for the difference between the groups (95% CI for the difference)” rather give the mean difference between the groups with 95% CI. The p-values will then be surplus.

Thank you, we preferred to use the p values with the 95% CI for the difference as in our experience, we have seen that people who are not very familiar with statistics prefer to see the p values. If however the editors and you feel that we should change the tables, we will do that.

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