Author’s response to reviews

Title: Could caregiver reporting adherence help detect virological failure in early treated Human Immunodeficiency Virus-infected infants? Experience from the PEDIACAM study in Cameroon

Authors:

Francis Ateba Ndongo (atebfranc@gmail.com)
Josiane Warszawski (josiane.warszawski@inserm.fr)
Gaetan Texier (gaetex1@gmail.com)
Ida Penda (idapenda@yahoo.fr)
Suzie Tetang Ndiang (ndiangsuzie@yahoo.fr)
Jean-Audrey Ndongo (jeanndongo@yahoo.fr)
Georgette Guemkam (guemgeorg@hotmail.com)
Casimir Ledoux Sofeu (scl.ledoux@gmail.com)
Kfutwah Afumbom (kfutwah@pasteur-yaounde.org)
Albert Faye (albert.faye@rdb.aphp.fr)
Philippe Msellati (philippe.msellati@ird.fr)
Mathurin Cyrille Tejiokem (temacy@yahoo.fr)

Version: 3
Date: 6 July 2015

Author’s response to reviews: see over
RESPONSE TO REVIEWERS

Article title: Could caregiver reporting adherence help detect virological failure in early treated Human Immunodeficiency Virus-infected infants? Experience from the PEDIACAM study in Cameroon

MS: 54 39 68 26 91 42 18 13

A-) ANSWERS TO REVIEWER 1 (MALIK COULIBALY)

1) ABSTRACT

No comment has been done.

2) INTRODUCTION

The reviewer commented that the assertion “viral load is the best marker of adherence to cART” is true when considering antiretroviral naïve patients.

In page 4, lines 11-12: we have modified the phrase as following (written in italics): “Viral load measurement is the best marker of response to cART which is strongly reflective of adherence to cART in patients whose strains are susceptible to antiretroviral treatment they are receiving.”

3) METHODS

The reviewer asked why we considered the caregiver’s recall of missed doses until 14 days, when it is advisable to avoid going beyond seven days because of bias related to memory.

In the whole structure of the adherence questionnaire, both recall of missed doses in the past 3 days and the past 14 days are mentioned. But in this study, we only considered caregiver recall of missed doses in the past 3 days.
The reviewer mentioned that in page 8, line 5, there is a typo: it is M24 instead of M12.

We made revision (written in italics) according to the reviewer’s suggestion.

4) RESULTS

- The reviewer noticed that there was not any distribution of the study population with respect to the antiretroviral regimen.

In page 9, lines 5-6, we added the following phrase (written in italics): “Respectively 34% and 64% started cART with nevirapine-based and lopinavir-based regimens”.

- The reviewer suggested that we present the table of logistic regression which shows no significant association between reported difficulties and missed doses.

Importantly, most of the caregivers reported no difficulty in administering cART dose, that is 140/143, 119/122 and 76/79 respectively at M3, M12 and M24. Thus, in page 11, lines 7-8, we suppressed the assertion that emphasized the absence of association between reported difficulties and missed doses (written in italics).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M3</td>
</tr>
<tr>
<td>Difficulty in administering cART doses</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>6.5 (0.6-73.8)</td>
</tr>
</tbody>
</table>

NA: Not Applicable because of colinearity; in fact, all the infants whom the parent declared difficulty in administering cART were adherant.
In table 3, page 19, line 11, the reviewer found errors when calculating the LR+ and the LR- of the “#2 cumulative missed (B)” at M12.

We made revisions (written in italics) according to the reviewer’s suggestions.

The reviewer recommended that titles of the figures 1 & 2 should be under the figures instead of above and the vertical segment of line in table 2, page 17, line 4, should be removed.

Revisions were made according to reviewer’s suggestions (written in italics).

5) DISCUSSION

The reviewer wondered why missed dose reporting was not significantly associated with any reported difficulties and if it is related to a lack of power.

Most of the caregivers reported no difficulty in administering cART dose, that is 140/143, 119/122 and 76/79 respectively at M3, M12 and M24. Thus we suppressed that assertion.

The reviewer wondered if we could comment on how the presence of antiretrovirals in 7 patients out of 14 tested may affect the reliability of using viral load to assess adherence to antiretroviral

Viral load measurement is a marker of response to cART which is strongly reflective of adherence to cART only in patients whose strains are susceptible to antiretroviral treatment they are receiving. But the objective of the study is to assess the reliability of using caregiver adherence reporting to assess adherence to treatment.

The findings from this study strongly suggest that in the majority of cases, patients whose caregivers report high adherence and have virological failure have resistance mutations (see page 12, lines 16-22, written in italics).
The reviewer noticed a possible bias in the adherence assessment through questionnaires due to the possibility of the respondents to be influenced by their health care providers. Particularly, physicians represented 34.8% of the interviewers.

According to our study analyses, there was no association between caregiver reporting of missed doses and the type of health worker, particularly at M12 and M24 (see page 11, lines 7-8, written in italics).

The reviewer suggested mentioning a limit related to our method of missed dose assessment described in page 7, lines 21-19, it is stated: “When a quarterly visit was performed but the adherence questionnaire not completed, we considered the previous number of missed doses for that particular visit”. He perceived limitations if the reasons why the patients attended the quarterly visit with an uncompleted questionnaire, were related to poor adherence specifically at that particular visit, while they performed well in the previous visit.

The questionnaire was not self-reported. Rather it was administered by health care providers. Thus an uncompleted questionnaire was likely due to problems of health care organization in the health facility (e.g. health care forgetting to administer the questionnaire, questionnaire lost, infant lost to follow up after blood drawn in the lab before medical consultation or drug delivery, etc).

B-) ANSWERS TO REVIEWER 2 (CONSUELO BECK-SAGUE)

1) ABSTRACT

- The reviewer suggested nuancing the following statement as there is a wide range of costs actually paid by African countries: «Unfortunately it is too expensive for resource-poor settings».

Thus we made the following revision (written in italics): “Unfortunately it is difficult to access in many resource-poor settings”.

- The reviewer suggested nuancing the following statement since adherence is not actually a diagnosis as such (presence or absence of illness): “We aimed to measure the diagnostic value of caregiver reporting adherence for detecting virological failure in routine practice during the first 2 years after cART initiation in infants.”
Thus we made the following revision (written in italics): “We aimed to measure the performance of caregiver reporting adherence for detecting virological failure in routine practice during the first 2 years after cART initiation in infants”.

- As suggested by the reviewer, we defined the virological failure in the abstract as following (written in italics):

  “Virological failure was defined as having a viral load≥1000 cp/mL at 3 and 12 months after cART initiation or having a viral load≥400 cp/mL at 24 months after cART initiation.”

- As suggested by the reviewer, we changed the following statement “However, cumulative missed dose may be useful for the detection of virological success, particularly after 12 months of cART, given its high negative predictive value” to:

  “However, the cumulative missed dose measurement may be a reliable predictor of virological success, particularly after 12 months of cART, given its high negative predictive value”.

2) INTRODUCTION

- The reviewer recommended nuancing the following statement in page 4, lines 11-13: «Viral load is the best marker for adherence to cART».

  Thus we made the following revision (written in italics): “Viral load measurement is the best marker of response to cART which is strongly reflective of adherence to cART in patients whose strains are susceptible to antiretroviral treatment they are receiving.”

- In page 4 line 13, we changed the following statement “…but is too expensive for routine use in resource-limited settings” by:

  “But it is difficult to access for routine use in many resource-limited settings”

- In page 4 line 20-24, we changed the following statement “…There is a corresponding need for reliable methods, cheaper than viral load determinations, for assessing infant adherence to cART in routine practice” to:
“...There is a corresponding need for reliable methods, easier to access than viral load determinations, for assessing infant adherence to cART in routine practice”

- In page 5, line1, we changed the following statement “The main objective of this study was to assess the diagnostic values of caregiver adherence reporting questionnaires for detecting virological failure in routine practice during the first 2 years of cART in infants in Cameroon” to:

“The main objective of this study was to assess the performance of caregiver adherence reporting questionnaires for detecting virological failure in routine practice during the first 2 years of cART in infants in Cameroon”

3) METHODS

- In page 5, line 11, the reviewer recommended to use “The inclusion criteria” in the following statement “The inclusions in PEDIACAM were organized in two phases and are described elsewhere (18)...”

We suggest not making change in the statement. Here, by “The inclusions”, we mean “The recruitments” in a phase of the Pediacam study.

4) RESULTS

- The reviewer claimed some clarifications in page 17, Table 1, “CD4 count (%) at cART initiation (median, IQR)”: Indeed, 23 the median % of lymphocytes that are CD4+ and the IQR is 15-32%. We also added a definition of CD4 in the table 1 legend (written in italics).

- In page 18, table 2, “Viral load (cp/mL)”, the reviewer suggested that “[400-1000]“ should be “400-1000” or “[400-1000]“.

We propose no change because 400 is included in the interval while 1000 is excluded from the interval.
- In page 18, table 2, “Accompanied by”:

We made correction by changing “grand-mother” to “grandmother”.

- In page 18, table 3, title, the reviewer suggested to modify the title as following:

  “value of reported adherence for detecting virological failure in HIV-infected infants treated early by cART for at least 3 months”.

  We made revision but we would rather suggest “Performance of reported adherence for detecting virological failure in HIV-infected infants treated early by cART for at least 3 months”.

**5) DISCUSSION**

- In page 12, lines 3-4, we suppressed “low” in the following statement “Here, prevalence of virological failure was **low**: 47.8% at M3, 23.8% at M12 and 27.9% at M24, which explains the high NPV. A cohort study in Uganda reported that 28.8% (17/59) of children had viral loads #1000 copies/mL at M12, and this is consistent with our findings (20).”

- In page 12, lines 15-22, we modified the following statement “Other children were classified as “adherent” although they showed virological failure at M12 or M24, leading to false negative cases and subsequently to decreased sensitivity, NPV and LR+” to:

  “Other children were classified as “adherent” although they showed virological failure at M12 or M24, which would be considered false negatives, reducing the sensitivity, NPV and LR+ of caregiver adherence reporting as a test for virological failure”.

- In page 13, lines 1-3, we suppressed “resistance to ARV” in the following statement “Other factors which were not assessed by our study may be involved, such as resistance to ARV...”
We also modified the comments in page 12, lines 17-22 and page 14, lines 8-9 (written in italics).