Author's response to reviews

Title: A longitudinal evaluation of the impact of a polylactic acid injection therapy on Health Related Quality of Life amongst HIV patients treated with anti-retroviral agents under real conditions of use.

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Author's response to reviews: see over
Response to Reviewers

Article: A longitudinal evaluation of the impact of a polylactic acid injection therapy on Health Related Quality of Life amongst HIV patients treated with anti-retroviral agents under real conditions of use

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Dear Dr. Armstrong,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the link below. Do let us know if you have any problems opening the file.

Referee 1:  
http://www.biomedcentral.com/imedia/1040635160784689_comment.pdf
Referee 2:  
http://www.biomedcentral.com/imedia/5877139588084092_comment.pdf

Editor's comment:

"Although the decision of one of the reviewer is "Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)" I request the authors not to ignore the comments but to reply to all of them as minor, but mandatory minor revision."

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1. Editor’s request -- Please also include the details of your ethics approval within the manuscript.

Page four, Method, Design updated to read (new line in bold):

This trial was an observational, longitudinal, multicenter, open label study performed in France. The study did not alter patients’ usual medical management nor affect their physical or psychological integrity nor require specific monitoring visits. Indirectly nominal data concerning patients and nominal data concerning observer doctors were collected. A participation consent form was signed jointly by patient and observer doctor. The study was approved by the Paris Ile de France 4 Ethics Committee, Paris, France. The study was conducted in compliance with the Helsinki Declaration\(^{17}\), with the French Data Processing and Liberties Law no 78.17 of 06.01.1978, received a favourable opinion from the CCTIRS (Consultative Committee on Data Processing in Research in the field of Health), and was authorised by CNIL (National Commission on Data Processing and Liberties).

REVIEWER 1

Reviewer's report
Title: A longitudinal evaluation of the impact of a polylactic acid injection therapy on Health Related Quality of Life amongst HIV patients treated with anti-retroviral agents under real conditions of use.

Version: 1 Date: 8 August 2012
Reviewer: Jose JC Catalan
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: no competing interests

Reviewer's report:
This is well conducted clinical research project, and its results are sound and consistent. A couple of comments on methodological aspects of the study.

1. While the study design is that of an open trial, it would have been helpful and not too difficult to have used a 'wait group' design, using the participants as their own controls by asking them to complete the outcome instruments on entry and some time later, before actually starting treatment. I suspect it would not have affected the results, but it would have been a more elegant design.

Thank you for the comment.

2. The ABCD validation has not been published yet. It would be important to know from the authors what the state of scientific review of this instrument is. Ideally, the paper should be available for perusal.

A validation article has actually been published, number 15 as cited in the manuscript. A draft manual is also available from the lead author.


3. The authors do not comment, unless I have missed it, on gender differences. It would be important to know if they found any differences between men and women in any of the measures at follow up.

As shown in the results 87% of the study population were men. With this in mind we did not address sex differences as a point of interest. This is now addressed with a sentence in the study limitations section (final paragraph of discussion), which reads: “Thirdly, most participants were male hence the findings best represent the treatment experience of men rather than women.”
Reviewer's report
Title: A longitudinal evaluation of the impact of a polylactic acid injection therapy on Health Related Quality of Life amongst HIV patients treated with anti-retroviral agents under real conditions of use.
Version: 1 Date: 18 September 2012
Reviewer: Richard Harding
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'

Reviewer's report:
- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Background

1. You should spell out NI and PI

Done.

2. I think the word substantive should be changed? Do you mean substantial?

Yes. Corrected.

3. It is quite difficult to match the objectives in the abstract and main paper as they are written as 1-4 then main + 1-3.

Objectives stated in abstract are now clearly matched to objectives stated in main paper. The final paragraph of the Background section now reads - “The objectives of this study were four-fold: (1) The primary objective was to describe the impact of NEW-FILL® on the quality of life of patients treated with antiretroviral agents, using the lipodystrophy-specific ABCD quality of life self-questionnaire(14,15). The secondary objectives of this study were: (2) to describe the efficacy of NEW-FILL® based on photographs taken before the first injection, 2 months after the last injection session, and then, if applicable, 12 and 18 months after the last injection session; (3) to describe overall efficacy of treatment with an “Overall Treatment Effect” (OTE) scale(16), (4) to describe safety of NEW-FILL® in the short, medium and long term.”

Paragraph 3 of Results now begins – “The first and primary objective of …”
Paragraph 5 of Results now begins – “The second objective …”
Paragraph 7 of Results now begins – “The third objective …“
Paragraph 9 of Results now begins – “The fourth objective …“

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

This study addresses an important clinical issue and uses interesting methods to measure outcomes.

**Background**

4. Can you justify the claim that lipodystrophy is one of the main effects of treatment in the medium and long term with reference to the literature?

This claim is addressed in paragraph 2 of the Background:

“Many cross-sectional studies have demonstrated the prevalence of lipodystrophy ranging from 18 to 80% in patients who received antiretroviral therapy\(^2,3,4,5\). It is estimated that about 50% of patients develop lipodystrophy after one to two years of exposure to multiple drug therapy including a Protease Inhibiter (PI)\(^6\).”

5. Can you briefly discuss what is known to date in effectiveness of fillers/other management of lipodystrophy? You discuss it at the end of the paper, but if you are presenting a new evaluative study you need to make a substantive argument of what this will add to the existing literature of effectiveness.

As the reviewer notes, the study results are discussed in the context of treatment alternatives in the Discussion section. The authors are of the opinion that this does not need to be repeated in the Background section.

We have however added a final sentence to the 4th paragraph in the Background section, which leads directly to the primary aim in the 5th and final paragraph:

“In France, L-polylactic acid (NEW-FILL\(^6\)) is a medical device which obtained a favourable opinion from the Commission for Evaluation of Products and Services (CEPP)\(^13\) for reimbursement in correction of facial lipoatrophy in HIV-positive patients treated with antiretroviral therapies. **The impact of this treatment on patients’ quality of life has not previously been addressed.**”

6. In terms of objectives can you clarify your safety objective in relation to any prior evidence from clinical trials? What new information is necessary?

A number of NewFill studies have reported safety / adverse event data. We simply sought to make our data similarly available.
Objective 4 (final para background) now reads: (4) to contribute further data regarding the safety of NEW-FILL® in the short, medium and long term.

Discussion paragraph 6 now commences as follows: “Treatment safety data concurred with the findings of previous studies\(^{(26,27,28,29)}\).”

**Results**

7. It is confusing talking about “the first secondary objective”.

Corrected. Reference to all objectives in body of manuscript changed as per Reviewer Comment 3.

**Methods**

8. You call this study a trial. In what sense is it a trial, and if it is what phase trial/design is it?

Corrected. The two references to ‘trial’ where they describe our study have been replaced with ‘study’. It is clearly indicated that this was an observational, longitudinal, multicenter, open label study performed in France.

9. It is difficult to interpret the sentence:

“The study did not alter patients’ usual medical management nor affect their physical or psychological integrity nor require specific monitoring visits. Indirectly nominal data concerning patients and nominal data concerning observer doctors were collected.”

Is that that you were following patients under usual care, and that no additional visits were necessary, but that you did ask for additional information during usual care visits (which would have increased visit time?

Yes your interpretation is correct. This sentence, in Methods, Design, para 1 has been corrected to read:

“… The study followed patients during their usual care routine. Additional information pertaining to the study was asked for during usual care visits. It did not alter patients’ usual medical management nor affect their physical or psychological integrity nor require specific monitoring visits…”

This and a number of other clarity issues you have raised stem from translation issues. English is a second or third language for some authors, while others have limited or no proficiency in English.

10. What do you mean by nominal data?

This is a translation issue. Nominal data refers in France to patient and doctor sociodemographic categorical data. We have deleted the reference to nominal data.
Exact sociodemographic characteristics are named where referred to in the manuscript.

11. What are observer doctors, at this stage in the paper it is not yet described so cannot be understood by the reader.

Observer doctors were those recruited into the study as co-investigators. We thought this self-explanatory at the time. We have replaced the two references to ‘observer doctors’ in the manuscript to read ‘Investigating doctors’.

12. What is a systematic patient diary?

The ‘systematic patient diary’ is the name given to the patient file that investigating doctors kept for the purposes of this study. It included dates of visits, patient checklists, patient photos and so forth. We have deleted reference to it as it may be confusing and adds no value to the study.

13. How did you identify and approach doctors?

More Information to this effect is now provided under Method, Recruitment of doctors and patients, the first para of which now reads: “Thirteen ‘investigating’ doctors were recruited from 13 centres where NEW-FILL® treatment was provided. Investigating doctors were recruited from a list of all doctors trained in the injection technique who had treated at least one patient with NEW-FILL®.”

14. What was the study powered for if it was a trial, and what difference were you looking for?

This was an observational study rather than trial. This has been corrected in the manuscript.

15. Has the ABCD QoL tool been validated in France?

It has been validated in France (linguistically and psychometrically) but the data remains in an unpublished report tagged for development. The ABCD has been validated in a published study using an Italian sample. See article 15 in the references section.

16. What do you mean it was a non-interventional study?

It was observational study. We have corrected this in the manuscript.

17. Can you explain what you mean by confirmatory analysis?

‘Confirmatory’ has been deleted so as not to be confused with specific forms of statistical analyses. It was a simple reference to cross-checking a given set of findings against another.
18. The analysis plan refers to qualitative variables but it is unclear what these are?

In France, sociodemographic variables or ‘Nominal’ variables are also sometimes referred to as Qualitative variables. It is clearly unnecessarily confusing, so all references to Nominal and Qualitative variables have been deleted.

19. The analysis plan does not describe which time points you are referring to, how does time point fit into your analysis plan?

Method, Statistical methods paragraph has now been reworked to be inclusive of time points:

“Statistical analyses were performed with SAS software, version 8.2 (19). Data were described in terms of sample size, mean, standard error, percentage by modality, response, and number of missing data, pre-treatment (time 1) and post-treatment (time 2: 2 months; time 3: 12-18 months). Evaluation of quality of life was performed based on a score calculated according to recommendations of the ABCD questionnaire. Wilcoxon t-tests were used to determine the significance of within-group changes over time in QoL component scores between the inclusion or pre-treatment visit (time 1) and post-treatment visits (time 2, time 3). Determination of the minimal important difference in quality of life was derived from calculation of the pre-treatment (time 1) and post-treatment (time 2, time 3) change in QoL score that corresponded with an OTE rating (2 or 3) of a condition ‘a little improved’ or ‘somewhat improved’. Evaluation of photographs pre- (time 1) and post-treatment (times 2,3) were performed by a committee of experts according to the scale for classification of lipoatrophy. Frequency of reported side effects were calculated.”

20. How did you handle missing data?

This is now better explained in the Results Paragraph 2: "Data on 911 sessions of injections were collected on the 230 patients, i.e. a mean of 4 sessions of injections per patient. Over half of the patients (51.3%) had 5 sessions of injections of NEW-FILL®. Injection sessions most often involved the cheeks (98.9%) and temples (37.7%). Other facial areas were a rarer focus (7.7%). One hundred and ninety-seven patients had an evaluable ABCD questionnaire at inclusion (at least 50% of items completed), an evaluable ABCD questionnaire at one monitoring visit and an OTE questionnaire filled out at the same monitoring visit. One hundred and seventy-seven patients had a photograph considered evaluable at inclusion and at the monitoring visit at 2 months. A photograph was considered evaluable if it could be classified by the expert committee according to the lipoatrophy grading system. Patients for whom the course of NEW-FILL® was not followed by a monitoring visit at 12-18 months after the last injection session or whose evaluation visit at 12-18 months was not evaluable were considered as lost to follow-up. Of the 230 patients included, 124 were lost to follow-up.”

21. The analysis plan is generally very brief, what type of within-group analysis did you perform?
Sentence added to Methods, Statistical Methods: “Wilcoxon t-tests were used to determine the significance of within-group changes over time in QoL component scores between the inclusion or pre-treatment visit (time 1) and post-treatment visits (time 2, time 3).” Note that these analyses were already referenced, but only in Table 2.

Discussion

22. What do you mean that the ABCD scores are actually comparable to?

The reviewer is presumably referring to the last sentence of Discussion paragraph 2 in which we state: “Similar studies using generic QoL measures such as the SF-36 have sometimes failed to find significant treatment gains\(^{(22)}\), while others have failed to show QoL differences between patients with and without lipodystrophy\(^{(4)}\). On the other hand, studies using the ABCD have reported comparable results\(^{(23,24)}\).”

We have changed that last sentence to read: “On the other hand, studies using the disease-specific ABCD QoL measure have reported results comparable to those found here”.

23. How do you conclude that changes are “a little improved” or “somewhat improved”? Where do these labels originate?

These labels originate from the Overall Treatment Effect scale used in our study, reference 16 in the manuscript:


24. You make a fair methodological point that, in light of no comparative group, it is true that this problem does not spontaneously improve. However, your main argument with respect to outcomes is that quality of life is important, and this may indeed regress to the mean. Please discuss. This is also relevant to the Abstract where you state that QoL changes are attributable to the treatment; the design means you cannot make that attribution.

It is true that we have no control group, therefore can not argue solely on the basis of this study for treatment causality. Reference to ‘attributable’ in the Abstract-Conclusion and Discussion have been removed. However, lipoatrophy does not improve spontaneously, nor consequently does lipoatrophy–specific QoL. And both doctor ratings of lipoatrophy visability and patient ratings of lipoatrophy–specific QoL did improve significantly following treatment as measured in the short and long-term post-treatment. We can therefore state that QoL and lipoatrophy visiblity improved in the immediate months following NewFill treatment and that improvements were maintain 12-18 months post-treatment.
The related Abstract sentence (in para 4) now reads:
“Improvements to quality of life and diminished lipoatrophy visibility were observed in the months immediately following NEW-FILL® treatment and were maintained 12-18 months post-treatment”.

The related Discussion sentence (in para 7) now reads:
“As shown here, improvements to lipoatrophy occurred following NEW-FILL® treatment in ways that were meaningful and recognisable to both doctor and patient.”

25. Do you think any visible adverse treatment events might influence the visual scoring?

Yes. Visible adverse treatment events would be rated in the direction opposite to improvement. As indicated in the Method, Data collection, Lipoatrophy grading system, photographic slides (each containing 3 views: 1 front, 1 right side, 1 left side) were submitted in random order, blinded (before treatment/after treatment or after treatment/before treatment), and without indication of the injection site.

26. Why do you think there was so much missing data, even at baseline?

We really don’t know. Patients could get the same care without choosing to participate in the study, or without completing their participation in the study. NewFill is available to non-study participants and costs are completely covered by French social security. As it was an observational study imbedded in the usual care routine the patients were under less pressure or incentive to participate or complete participation.

27. In the discussion you make the important statement that 5 prior studies have shown comparative effectiveness of this treatment, which begs the question of why this observational study adds something new, what is substantive? Particularly in light of your safety objective, but do discuss all objectives.

That is a bit of a simplification. As argued in the Discussion, similar studies using generic QoL measures such as the SF-36 have sometimes failed to find significant treatment gains(22), while others have failed to show QoL differences between patients with and without lipodystrophy(4). On the other hand, studies using the ABCD have reported comparable results(23,24). Our study adds support to the use of patient-reported QoL measurement using the ABCD when lipodystrophy is present. An effective patient-reported QoL tool may be a better indicator of treatment need than medical assessment procedures commonly used in clinical trials such as DEXA scan, bioimpedance or sonography. For instance low sensitivity poses a problem for the use of sonography to detect LD in the clinical routine as a single exam(24).

With respect to the safety objective, we felt it worthwhile to contribute our data to the existing pool.
28. It is difficult to support your final statement that doctors report satisfaction with the treatment when no data were collected on this.

This sentence has been removed.

29. **In tables spell out SEM; again the analyses in the tables are not adequately described in the methods.**

For Tables 1, 2 and 3, SEM is now spelled out as Standard Error of Measurement. Table 2 Wilcoxon tests are now described in Methods, Statistical Methods. Table 3 Facial lipoatrophy (FL) grades are referred to in Methods, Statistical Methods and fully described in Data Collection, Lipoatrophy grading system.