Author's response to reviews

Title: Predictive factors of virological success to salvage regimens in HIV-1 infected children

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Author's response to reviews: see over
Dear Sir,

RE: BMC Manuscript 3903641221255686 (Larru et al. Manuscript entitled: PREDICTIVE FACTORS OF VIROLOGICAL SUCCESS TO SALVAGE REGIMENS IN HIV-1 INFECTED CHILDREN)

Thank you very much for your e-mail of March 12, 2007. Please find enclosed a point-by-point response to the reviewers’ comments and the new revised version of our manuscript. We hope that the current revised version of our manuscript is acceptable for publication. Please feel free to contact us regarding any further questions about our work.

Thank you very much for your consideration. We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Beatriz Larrú Martínez, Dr.
**Reviewer 1:**

**Major Compulsory Revisions:**

1) We agree with the referee in that. Now, we incorporated in Methods: “The adherence of antiretroviral drugs included in the savage regimen, was measured by each paediatrician by pill count and through interviews with their parents or tutors”.

2) We agree with the referee in that. As we carried out a retrospective study we only include those children who have a baseline resistance test but the salvage regimen was not homogeneous among the population and sometimes it includes drugs which were not considered as susceptible by the virtual phenotype. The fact that there are fewer drugs available for children than for adults could explain why sometimes the savage regimens not always include susceptible drugs. That is why we carried out this study to assess the usefulness of new tools like virtual phenotype in the management of HIV-infected children. We included in Methods: “There was not a uniform approach regarding antiretroviral drugs included in the salvage regimen. Instead, each paediatrician administered the appropriate ART regimen and changed the drugs according to his/her interpretation of the children data” to clarify this idea.

3) We agree with the referee in that. Now, we incorporated in Discussion “Moreover, we did not measure other factors such as pharmacokinetic or drug interactions which might have had influence in the virological success of our population”.

4) We agree with the reviewer in that but our study included as many patients as we could because it is a retrospective one based in a real life situation. However we added in Discussion: However, more studies with higher sample sizes which evaluate the usefulness of new tools like virtual phenotypic resistance test or the combination of pharmacokinetics parameters and resistance test are needed to improve the management of HIV-infected children.

**Reviewer 2:**

**Minor Essential Revisions:**

1) We agree with the reviewer and we change the paragraph into: “All children had been exposed to at least one PI before the first determination. The proportion of children who have been treated with different PI were as follows: Nelfinavir (NFV) (78.8%), Lopinavir/ritonavir (LPV/rit) (36.4%), Ritonavir (RTV) (30.3%), Indinavir (IDV) (21.2%), Saquinavir (SQV) (21.2%) and Amprenavir (APV) (6.1%). The number of PI that the children have taken before the baseline determination was: 48.6% had taken 1, 24.2% had taken 2, 15.1% had taken 3, 9.1% had taken 4 and 3% had taken 5. At baseline all the children take a PI as part of the savage regimen. At time of the analysis, 60.6% were using NFV, 30.3% LPV/rit, 6.1% IDV and 3.0% SQV/rit”.

We only described the use of boosted-PI because it is a predictive factor in our analyses but we could include all the savage regimens employed if the reviewer thinks that this is appropriate.
2) We agree with reviewer and we have changed this all over the test.

3) We agree with the reviewer and we change this in the Results and in Table-1 and Table-2, where we also explained which mutations are considered as NAMs.

4) We agree with the reviewer and we incorporated in Table-2: “No. active PIs in the salvage regimen according to virtual phenotype”.

5) We agree with the reviewer and we incorporated in Table 1: “Results are expressed as median (IQR)”.

6) We apologize for the mistake and we have delete references 20 and 21 in the text and we have bought up to text reference 12.

- **Reviewer 3:**
  We appreciate his opinion but we disagree with the reviewer about his opinion about the usefulness of resistance test to predict virological response as some of the authors included in our bibliography have studied.


- **Reviewer 4:**
  We really appreciate her suggestions.

  1) We agree with the reviewer and we changed the Title page and we also include the author’s degree in the title page.

  Predictive factors of virological success to salvage regimens containing protease inhibitors in HIV-1 infected children

  Salvage regimens in HIV-1 infected children

  2) We agree with the reviewer and we change in the Abstract:

  - A multicenter, retrospective, observational study was conducted in children who received rescue salvage antiretroviral therapy after virologic failure
  - A total of 33 children met the inclusion criteria and were included in the analysis.
  - The median viral load (VL) and median percentage of CD4+ at baseline was 4.0 HIV-RNA log copies/ml and 23.0% respectively.
The median duration that children were taking the new rescue regimen was 24.3 weeks (23.8-30.6).

Overall, 47% of the 33 children achieved virological response at 24 weeks.

We changed infants into children throughout the text.

We included the p value.

Moreover, the mean number of susceptible drugs...

Eighteen children were rescued with a regimen containing a boosted-PI and virological response was...

3) We agree with the reviewer and we changed in the Background:

- These children are surviving through adolescent into adult life...
- However, children taking antiretroviral therapy tend to present with higher plasma viral...
- We added why boosting PI shows greater activity: “The use of co formulation of PIs with a fixed dose of ritonavir (rit) has shown a greater activity in both antiretroviral-naïve and treatment experienced HIV-1 infected children than previous PIs because of its pharmacokinetic advantages due to low-dose of rit which enhance the antiretroviral activity of the other PI”.

4) We agree with the reviewer and we change in Methods:

- When PI-containing regimens were used as...
- We changed copies per ml into copies/ml throughout the text

5) We agree with the reviewer and we change in Results:

- Distribution according to sex was...
- We spelt out PI when they were not abbreviated earlier
- At time of the analysis, 60.6% were using NFV, 30.3% LPV/rit, 6.1% IDV and 3.0% SQV/rit.
- The median CD4+ cell counts and percentage at baseline were 707.0
- We included decimals for all values.
- We included: M184V was found in 11 children (33%); 3 of them (30.3%) were resistant to Abacavir and 1 of them (15.2%) was resistant to Tenofovir according to the virtual phenotype. At baseline, 42.4% of children have NNRTI mutations; 30.3% have the K103N and 15.2% the Y181C.
- We added: Virological response defined as plasma HIV-RNA reductions greater than 1 log and/or VL less than 50 HIV-RNA copies/ml was achieved in 46.9% of children in the first 24 weeks of follow-up. However, 66.6% of them reached undetectable viremia after 24 weeks of follow-up.
- We found the following differences...
- We only described the use of boosted-PI because it is a predictive factor in our analyses but we could include all the savage regimens employed if the reviewer thinks that this is appropriate.
- We added: In the univariate analyses, there was not association between the number of baseline protease resistance mutations and virological response. Moreover, there was also not association between virological success and RT resistance mutations, the previous length of antiretroviral therapy, previous length of PI exposure, number of PI previously received or rescue interventions with boosted-PI.
- We explained why we did not carry out this analysis in the Discussion: Our study has several limitations primarily due to the small sample size. We did not assess the relevance of other classes of antiretroviral drugs in the rescue...
regimen because HAART combinations were not homogeneous in the population as it is a retrospective study based in a real life situation.

- We added: None of them received a double boosting of PIs.

6) We agree with the reviewer and we change in Discussion:

- In this study, we evaluate the predictive factors of success when PIs are used as salvage therapy in a group of heavily pretreated HIV-infected children with virological failure.
- We rewrote first paragraph into: We found that nearly half of them achieve virological response after rescue interventions. Our results are similar to other studies which also have been carried among children in real life situations.
- We added: However, children usually have lower virologic response rates than adults due partially to lower treatment adherence leading to underestimation in the factors associated with virological response. Besides, the fact that viral load is higher among children than in adults, can lead to the development of resistance mutations which could reduce the effectiveness of antiretroviral drugs in further combinations.
- We added: However, more studies with higher sample sizes which evaluate the usefulness of new tools like virtual phenotypic resistance test or the combination of pharmacokinetics parameters and resistance test are needed to improve the management of HIV-infected children.
- We included: Our study has several limitations primarily due to the small sample size. We did not asses the relevance of other classes of antiretroviral drugs in the rescue regimen because HAART combinations were not homogeneous in the population as it is a retrospective study based in a real life situation. Moreover, we did not measure other factors such as pharmacokinetic or drug interactions which might have had influence in the virological success of our population

7) Table-1:

- As we have explained before we did not include in our analyses the NNRT use because of our small sample size and the fact that not all rescue regimens were homogeneous.
- In order to clarify the Table we did not include in the Table dates about M184V or susceptibility of TNF or ABC because we have explained before in the text and we do not include them as predictive factors of virological response in our analyses.
- We included decimals in the Table.

8) Table-2:

- We apologize for the mistake and we report our results of the logistic regression as OR instead of B-coefficient.
- We did not include all the variables in Table 2 because of our small sample size. However, we added in Discussion that other studies with higher sample sizes should be carried out to improve the management of HIV-infected children.