Author's response to reviews

Title: Predictors of First-Line Antiretroviral Therapy Discontinuation Due to Drug-Related Adverse Events in HIV-Infected Patients: a Retrospective Cohort Study.

Authors:

Mattia CF Prosperi PhD (ahnven@yahoo.it)
Massimiliano Fabbiani MD (massifab@alice.it)
Iuri Fanti Dr (iuri.fanti@gmail.com)
Mauro Zaccarelli MD (mauro.zaccarelli@gmail.com)
Manuela Colafigli MD (manuela76@inwind.it)
Annalisa Mondi MD (annalisamondi@hotmail.com)
Alessandro D'Avino MD (alessandro-davino@virgilio.it)
Roberto Cauda MD (rcauda@rm.unicatt.it)
Simona Di Giambenedetto MD (simona.digiambenedetto@rm.unicatt.it)

Version: 2 Date: 7 July 2012

Author's response to reviews: see over
Dear editor and reviewers,

We thank you for the competent feedback. We have now produced a revised version of the manuscript and we hope now it meets the requirements for publication.

Please find the detailed responses to reviewers’ comments as follows.

**Editorial Requests**

Kindly provide (within their manuscript) the specific name of the ethics committee which approved their study.

On page 5, 1st paragraph, 4th row, we wrote the following phrase: “All patients included in the data base had previously signed an informed consent to be included in observational studies. Access and data analyses of the CUSH data base are regulated by an institutional internal ethics committee and conform to Italian and European privacy legislations.” Note that the CUSH ethics committee is not defined by a specific name.

Please remove your qualifications from workflow.

The “Dr.” qualification (Dr. Mauro Zaccarelli) of the corresponding author was removed from the manuscript. If this was not the correction required, we kindly ask to clarify.

**Reviewer #1**

This retrospective analysis of causes of cART discontinuation has some flaws the authors must address:

**Major Compulsory Revisions:**

1. Abstract, Background: the verb should be have been better that is.  
   Corrected.
2. The temporal frame of the study is not stated in the abstract.  
   Added.
3. Abstract: when describing the K-M estimation, does it really mean survival or being free of adverse effects? This is repeated in page 8.
Being free of adverse effect (now specified also in page 8).

4. Abstract, conclusions are completely inadequate, and they do not reflect the objective of the work. They general and imprecise.
   Re-written, as suggested.

5. The first anti-HIV therapy is said to have been recorded in 1985. To my knowledge, AZT became available only in 1987.
   The first ART record was 1988 (as then stated in the results section). We apologize for the typo in the text.

6. The methods' section is particularly cumbersome in the part describing the lab cutoff levels. Should be drastically rewritten.
   We agree that the cutoff level description was cumbersome; therefore we moved the cut-off values in Table 2, where the lab markers are also summarized. Then the methods part has been shortened and sensibly cleared.

7. Methods: it is said the following time strata included 1998 and before (how much before?). Even when cART was unavailable?
   Also patients that were prescribed a suboptimal therapy, i.e. mono-dual therapies, and early three-drug therapies such as AZT+3TC+SQV have been analyzed. This included the time frame 1988 to 1998. However we also made a separate analysis analyzing all cARTs from 1999 onwards. Results have been shown for both analyses.

8. Then, in the results section, it is said that patients were included if first-line anti-HIV therapy was started between 1998 and 2010. The period 1998 and before is again considered in table 4.
   In the results section we showed incidence and RHs both for the population followed up in 1988-2010 and the population followed up after 1998. Since we did not find major differences both in incidence and prognostic factors, we merged the descriptive and inference results in Tables 1-4.

9. The number of patients by time is not specified.
   Now added in table 1.

10. The number of patients on drugs such as Atripla, Truvada and ATV seems quite low which clearly decreases the interest of comparisons. ART is badly specified.
    This is true and it might be also an explanation for which no appreciable RHs have been found with this encoding. That is why we defined 4 different encodings, specifying them also in table 1.

11. Table 3: The causes of cART discontinuation have not been previously defined.
We updated the methods section referring to table 3 for categories of discontinuation.

12. The HR for individual drugs have been adjusted by other drugs in regimen?
   Yes, this has been now clarified in the table footnote.

13. Fig 1. Here the K-M is defined as being free of AEs, which is contradictory to what is described in text.
   We addressed this issue. Now all across text is specified the KM being estimated as probability to be free from an adverse event.

Reviewer #2

Major Compulsory Revisions:

1. Methods: Include a flowchart
   A flow chart has been added.

2. Methods: clearly specify the data related to lost of follow up, death or interruption of treatment and also specify how many patients have a known stop date but unknown reason of stop and were excluded. Include the patients characteristics in each of the periods analyzed.
   Event definition and censoring criteria have been clarified. The number of first-line therapies with a known stop date and unknown stop reason have been included in the flow chart.
   Patients, events, PYFU, and therapy distributions have been calculated for each year or period and added wither in table 1 or in the new supplementary table 1.

3. Only patients with at least 3 antiretroviral drugs should be analyzed.
   This has been made in the sensitivity analysis of patients from 1999 onwards, including cART regimens.

Reviewer #3

The work by Prosperi et al was carried out to evaluate the predictors of first-line antiretroviral therapy discontinuation due to adverse events in HIV-infected patients. The manuscript is well-written and addresses the interesting and still controversial topic of tailoring cART on patient’s demographic, clinical and immuno-virologic characteristics. The research question is well posed and the methodology used is appropriate. In particular only few data are available in literature about the role of predictors of drug-
related adverse events which represent the major cause of therapy discontinuation even in late cART period. Recent international guidelines recommend early initiation of cART but no indication about what regimen to choose depending on patient profile are suggested. The attempt to identify a “patient-based profile” is of interest and could be of great support for clinicians in the strategic decision of first line cART. As expected, older antiretroviral compounds are associated with high risk of therapy discontinuations. However, efavirenz which is a first line drug was also associated with increased risk but only when co-administered with NRTIs different from fixed dose emtricitabine/tenofovir. Among more recent PIs, lopinavir and atazanavir seem to have no increased risk of discontinuations when compared with efavirenz+ emtricitabine/tenofovir. This “real life” result is of great interest particularly in those patients with baseline resistance and/or in those with psychiatric co-morbidities which do not indicate efavirenz prescription. The attempt to identify virus related predictors of toxicity apart from viral load, which has shown non association with therapy discontinuation, is also of interest and deserves further investigations in larger observational cohort which collect data regarding HIV subtypes.

As suggested by all tree referees, the discussion was revised, in particular the paragraph concerning limitations of the study was extensively re-written.

Reviewer #4

The objective of the study “to investigate predictors of first-line antiretroviral therapy discontinuation due to adverse events and their evolution in recent years” is a good choice and is sufficiently documented at the introduction. As a referee I really think that your work could be published although I would like to suggest some changes that may be need to edit the results and some part of the discussion for the article to be ready.

Major Compulsory Revisions:

1. Methods tell us that the cohort, with more than 4500 patients includes naive patients after antiretroviral therapy initiation, but in the study 1096 patients are included. The authors may explain the exclusion criteria for the rest of the patients in the cohort. I suggest including a figure with a flowchart for helping to understand better the study concept.

A flow chart has been added.
2. Also, I suggest that in the methods paragraph it should be more clearly specify the data related to lost of follow up, death or interruption of treatment and to specify how many patients have a known stop date but unknown reason of stop and were excluded. The authors will help to understand if in table 1 include a description of patients characteristics in each of the periods analyzed.

Clarified both in the methods section and in the flowchart

3. The study includes HIV infected patients that started their first antiretroviral therapy from 1985 to 2010. The study includes patients before the era of HAART and also patients with HAART that includes first and second generation antiretroviral drugs. I believe that only patients with at least 3 antiretroviral drugs should be analyzed.

This has been made in the sensitivity analysis, in which patients prescribed a cART only from 1999 onwards were included.

Minor Essential Revisions

The first paragraph of methods: “patients included in the study had previously signed an informed consent to be included in observational studies.” should be change to patients included in the DATA BASE had previously signed an informed consent to be included in observational studies.

Corrected.