Author's response to reviews

Title: Single tablet regimens are associated with reduced Efavirenz withdrawal in antiretroviral therapy naive or switching for simplification HIV-infected patients.

Authors:

Massimiliano Fabiani Dr (massi.fabbi@alice.it)
Mauro Zaccarelli Dr (mauro.zaccarelli@gmail.com)
Pierfrancesco Grima Dr (pierfrancescogrima@yahoo.it)
Mattia Prosperi PhD (ahnven@yahoo.it)
Iuri Fanti Dr (iuri.fanti@gmail.com)
Manuela Colafiglì Dr (manuela76@inwind.it)
Alessandro D'Avino Dr (alessandro-davino@virgilio.it)
Annalisà Mondi Dr (annalisamondi@hotmail.com)
Alberto Borghetti Dr (al.bor86@gmail.com)
Massimo Fantoni Dr (massimo.fantoni@unicatt.it)
Roberto Cauda Prof (rcauda@rm.unicatt.it)
Simona Di Giambenedetto Dr (simona.digiambedetto@rm.unicatt.it)

Version: 2
Date: 6 January 2014

Author's response to reviews: see over
To the Editor of BMC Infectious Diseases

Dear Sir,

Thank you for giving us the opportunity to revise the manuscript entitled “Single tablet regimens are associated with reduced Efavirenz withdrawal in antiretroviral therapy naïve or switching for simplification HIV-infected patients”. The manuscript has been modified following the reviewers’ advices and suggestions, and we have addressed the reviewers’ concerns as indicated in the point-by-point reply that you will find below. Changes in the manuscript have been highlighted in yellow. We believe that this revised version of the manuscript is improved thanks to the reviewer’s comments and we hope that you will find it suitable for publication in BMC Infectious Diseases.

Sincerely,

Dr. Mauro Zaccarelli
National Institute for Infectious Diseases “Lazzaro Spallanzani”,
Clinical Department,
Via Portuense 292, 00149 – Roma.
Telephone +3906555170368
Fax +3906555170260
Email: mauro.zaccarelli@inmi.it, mauro.zaccarelli@gmail.com
Reviewer: Nicola Gianotti

**Reviewer:** Conclusions (both at page 2 - abstract - and at page 9): the sentence "EFV co-formulated in STR was associated with lower ..." maybe misleading and hence should be rephrased as follows: "starting EFV co-formulated in STR was associated with lower ...."; in fact, the authors did not study a switch from STR to a regimen with the same drugs not co-formulated; thus their results could not necessarily apply (for instance) at switches from a branded STR to generic drugs.

**Answer:** both the sentences have now been modified as suggested.

Abstract, conclusions: “In our experience, starting EFV co-formulated in STR was associated with lower virological failure and higher adherence...”.

Page 10 (ex page 9), Conclusions: “In conclusion, our results demonstrated that starting EFV co-formulated in STR was associated with lower hazard of virological failure and with higher adherence...”.

**Reviewer:** In other words, the fact that starting EFV co-formulated in STR is associated with a lower hazard of virological failure and with higher adherence does not necessarily mean that patients tolerating well a STR will be certainly less adherent or will interrupt more likely treatment after switching to a regimen with the same drugs, not co-formulated. This issue should be addressed in the discussion.

**Answer:** the discussion was modified adding the comments suggested by the reviewer.

Page 9, first paragraph: “Our findings demonstrate that starting regimens with a higher pill burden can be associated with a higher risk of treatment interruption, mainly related to adherence, and
thus suggesting the benefit of maintaining STR. However, it should also be emphasized that not all patients tolerating well a STR will be certainly less adherent or will interrupt treatment after switching to a regimen with the same drugs, not co-formulated. The choice of the regimen should be tailored on individual patients, discussing benefit and potential risk of each decision”.

**Reviewer:** In the discussion, authors should also try to discuss the protective effect of a low nadir CD4 count on EFV interruption, which I think was quite unexpected.

**Answer:** comments related to CD4 nadir were added in the results and discussion.

Page 7, end of third paragraph: “The association of interruption with higher CD4 nadir was detected, after adjustment in experienced patients (HR: 1.09, 95% CI: 1.02-1.18, p=0.022) and not in naïve patients (HR: 1.03, 95% CI: 0.94-1.12, p= 0.54).”

Page 9, last paragraph: “In our analysis higher CD4 nadir was associated with higher risk of interruption. This association was detected only in the multivariable analysis, and can be interpreted with higher adherence in patients who achieved lower cd4 level, in particular experienced patients, in whom a low CD4 nadir at baseline was observed.”
**Reviewer: José-Ramón Blanco**

**Reviewer:** The major concern are the reasons for therapy-switching (virologic failure, previous toxicity,...).

**Answer:** As indicated in the methods (page 4, section “Patients included”), no one patient switched for virological failure, since they were included in the analysis only if they switched to EFV + 2 NRTIs for treatment simplification after virological suppression. A more detailed description of reasons for switching was added in the results.

Page 5, last paragraph: “Most subjects switching to EFV + 2 NRTIs were from protease inhibitor-based regimen (527, 90.4%); 14 patients (5.2%) switched from 3 NRTI regimen, 9 (3.3%) from nevirapine-based regimen and 3 (1.1%) from raltegravir-based regimen: all subjects switched in order to reduce the number of pills or frequency of drug administrations”.

**Reviewer:** Which were the main causes of treatment interruption?. Did you had missing data? How many patients died during the follow-up?. How many lost of follow-up?.

**Answer:**

a. the main causes of EFV interruption has now been reported in the results.

Page 6: “The main causes of EFV interruption were: CNS toxicity (n=37, 6.7%); hypersensitivity (n=15, 2.7%); metabolic toxicity (n=11, 2.2%); other toxicity (n=14, 2.5%); virological failure (n=30, 5.4%); patient wish/non-compliance (n=47, 7.9%)”.

b. the study was performed on the database of two centers that regularly and accurately collect data, so that there were no missing data for the variables used in the analysis.

c. only one patient died during follow up. This has now been specified in the results section.

Page 6: “One patient died by non-HIV related causes during follow-up”.
d. a better definition of how the last observation was managed was added. Methods. Page 5:

Observations were censored at the time of the last available visit or death, including patients lost in follow-up, who were classified as virological failure if the last HIV-RNA was detectable.

**Reviewer:** A high number of patients on treatment with EFV were IDU (only 6 with STR). Could some of the interruptions be related to methadone use?.

**Answer:** the term IDU refers to the way of acquiring HIV infection (risk factor); this has now been specified throughout the text. Unfortunately, no accurate data are available about current injecting drug use or methadone treatment. In the STR group the proportion of IDU patients was about half than that among non-STR patients, but this difference was not statistically significant (table 1). Moreover, the lower risk of interruption in the STR group was confirmed also after adjusting for IDU (risk factor).

We have now specified in the limitation section that the imbalance in the proportion of IDU could represent a potential bias.

Page 10: “… a higher, despite not significant, percentage of IDU was observed in the non STR group. This could have partly influenced the results; however, all these variables were adjustment factors in the multivariable model, thus at least partly accounting for this potential bias”.

**Reviewer:** Finally, the comparison in the subgroup analysis of STR could be limited by the number of patients with abacavir plus lamivudine backbone (n=42).

**Answer:** Following the observation of the reviewer, the data was modified excluding patients treated with abacavir/lamivudine.
Page 7, last paragraph: “Excluding patients not treated with a tenofovir-containing backbone and then comparing STR vs. OD-2 pills regimens (tenofovir/emtricitabine as backbone) (249 patients), a lower proportion of treatment interruption in STR group was detected (17.1% vs 34.7%, p=0.022).”

**Reviewer:** This study would benefit from focusing on unique aspects that let them a unique contribution to the literature. For example, which was the outcome of patients over 50 years?

**Answer:** Age was not associated with treatment interruption, even taking into account subgroups of patients categorized by age. In particular, as suggested, patients over 50 years (n=79) did not show a different risk of EFV interruption when compared to younger patients. A brief description was added at the end of the results.

Page 7: “Age was not associated with treatment interruption, even taking into account subgroups of patients: i.e. older age (>50 years) was not associated with EFV interruption.”
Reviewer: Laurent Hocqueloux

Reviewer: The main limitations of this work are that i. baseline characteristics of groups are not identical and ii. The number of participants in the main interest group is low (only 17% of all patients). I agree that multivariate analyzes can substantially attenuate these differences between groups, but it remains that patients in the STR group have been treated more recently (calendar years), are more likely to have been switched to this regimen (than to be naïve patients starting with), and received better tolerated backbone (TDF+FTC = 100% for STR group whereas one third of other groups received AZT+3TC). Moreover there is slightly less IVDU in STR group. All these factors could bias the comparison and I think only an analysis with propensity score-adjusted baseline characteristics could allow a reliable comparison between groups.

However, this study is of interest because, in the current environment where the provision of generic became a reality, it is important to demonstrate to decision makers (medical experts, health economists) that going back to separate pills risks to undermine the effectiveness of therapy.

Answer: we agree with the reviewers that the two groups were not completely matched for all characteristics at baseline. This could be a potential bias and it has now been better discussed in the limitation section. We have also tried to deal with it by adjusting for all the variables in the multivariate model and by performing subgroup sensitivity analysis (excluding IDU as risk factor, considering only patients treated with a 2-pills regimen and tenofovir containing backbone and analyzing only patients starting EFV from 2007). We have now reported the results of these analyses in the results section and their discussion in the limitation section: end of page 7.
The two groups of patients (STR and non-STR) were not completely matched for all characteristics at baseline; in particular, a higher proportion of naïve patients and a higher, despite not significant, percentage of IDU was observed in the non STR group. This could have partly influenced the results; however, all these variables were adjustment factors in the multivariable model and several subgroup sensitivity analysis were performed to account for this potential bias.

The usage of propensity score can be very useful in observational studies to overcome potential confounding by indication and to have a better causal interpretation of the variable of interest. However, in our study, the inclusion criteria were quite strict to and the covariates of interest had a homogeneous distribution over the population sample, which, even if not randomized, could be analyzed properly with a multivariable regression approach, as probably the propensity score re-weighting (or non-parametric re-matching) would have produced a uniform reweighting.