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.

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Author's response to reviews: see over
We thank again the editor and the reviewer for the competent feedback. Please find our detailed responses below.

Reviewer’s report

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

Version: 2 Date: 27 August 2012

Reviewer: Nacho Suarez

Reviewers report:

Major Compulsory Revisions

1. In table 1 the times periods (1988-1993, 1994-1998, 1999-2004, 2005-2010) are not corresponding with the time periods describe in methods (1998 and before, 1999 to 2002, 2003-2005, 2006 to 2008, and 2009 to 2010). The mistake must be fixed. Time periods were analysed using different strata, using ranges or specifically defined periods (such as those previously shown in the Cox). Also, a continuous numerical indicator was used. In all cases, the calendar year covariate was not showing a significant higher/lower risk of a toxicity event. Following the reviewers concern, in order to avoid confusion, we replaced the strata in the Cox regression with the numerical variable. But for sake of completeness, we have briefly reported that the results did not change by stratifying the calendar year. Note that the other RH of this model remain almost the same (changes at the second decimal level).

2. The Cox analysis has compared the combined variable of Nationality non-Italian/unknown vs Italian that can be a bias for mistake. I suggest comparing non-Italian vs. Italian and unknown vs. Italian.

Done as suggested.

3. The number of patients on drugs such as Sustiva+Truvada seems quite low to be the reference in the comparison for multivariate analysis.

Following the reviewer’s suggestion we changed the reference categories. By changing the reference categories, we found that any NRTI+PI/r combination (excluding Kaletra® and Reyataz®) showed an increased risk of adverse events as compared to any other NRTI+NNRTI intake (not including Truvada®, Sustiva®, or Atripla®), with a RH of 2.49, 95% CI 1.22-5.06, p=0.012. In addition, any NRTI+PI/r combination vs. Kaletra® and Reyataz® yielded a RH of 3.10, 95% CI 1.57-6.09, p= 0.001. We added this in the main text. We also kept the results using the other reference category because we thought it was interesting to compare with Atripla.

4. The number of patients with Atripla, Reyataz or any other NRTI + PI/r is small simples so I suggest not make the analysis by subgroups.

We agree, although the power may not be high, we believed it was worth testing, given the interest of comparing these two strategies, and since we also used other different drug
encodings with a higher discriminatory power (such as single compounds, that were as well shown in the results).

5. I suggest the authors to consider the analysis into: • 2NRTI+PI vs NRTI+NNRTI • 2NRTI+PI/r vs NRTI+NNRTI • any other or subtype vs NRTI+NNRTI

This analysis was also carried out (see methods page 6 and updated results page 9). For ease of clarity to Table 4 lists explicitly the two most relevant encodings, but a footnote discuss also the other encodings.

6. In the document the analysis of HR for individual drugs is not clear which drug is used as a reference.

We specified in the table that it is a binary encoding (i.e. presence of that particular drug in the regimen, yes vs. no)

Minor Essential Revisions

1. I suggest to authors to eliminate from methods the paragraph: “This stratification was made in order to analyze the possible role of the introduction in Italy of tenofovir (November 2002), Truvada® (September 2005), and Atripla® (October 2008.” Since the events mentioned have place at the end of the three periods (1999-2002, 2003-2005, 2006-2008

We understand that that stratification is questionable and in addition did not reveal anything different from a numerical fit or IQR stratification. We removed the phrase from the main methods and added just a brief phrase in the results section. Following the reviewer’s point (and considering also Major comment #1), anyway, we have removed this stratification from the main table and replaced with the numerical fit (Cox) or the range (bi-variate descriptive year/event in table 1). However, on our opinion it is important to show that we did not see any “breaking” period in terms of toxicity reduction/increase, whilst this might not be the general thought.

2. In table 4 the time periods have a mistake, 2004 vs. 2009 and 2010. Should be fixed.

Following also comment #1 we replaced the covariate with its numerical correspondent.

Discretionary Revisions

1. Bibliographic references 15-16 are not necessary to be included. I hope and wish that all my suggestions and commentaries helping you.

Removed as suggested, and 2 references added describing similar data collection policies of other study cohorts for toxicity analysis.