Author's response to reviews

Title: New Highly Active Antiretroviral drugs and generic drugs for the treatment of HIV infection: a budget impact analysis on the Italian National Health Service

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Version: 3
Date: 24 May 2015

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

Thank you for your valuable comments that have significantly helped to enhance the quality of our paper. Below you can find the responses to each of your comments; we hope to have been able to provide you with satisfactory amendments to the manuscript.

Yours sincerely,

Umberto Restelli

Reviewer's report:
The paper has some limitations but it deserves to be published with the formula "Essential Minor Revisions". The paper extrapolates trends on consumption and links them according to expert opinions, producing a sort of neutral forecasts on local drug market. So fourth, it has mostly a local importance. Some not compulsory suggestions are provided: in a BIA with a long time horizon, it is more appropriate to use a probabilistic or a double way sensitivity analysis; the paper has a scarce readability. I would suggest the typical pictures used in the scenario analysis (optimistic, reference and pessimistic scenarios).

We improved the readability of the paper with a revision by a British mother tongue expert. Concerning sensitivity analysis, we maintained the same approach, and we added a clarifying figure, as suggested by the reviewer.
Reviewer's report:
This is an important and timely paper that reports the modeled budget impact, over a 5 year timeframe, of a transition to generic antiretroviral drugs in the Italian National Health Service, and the introduction of new proprietary antiretroviral drugs.

Major Compulsory Revisions
None

Minor Essential Revisions
Methods: Paragraph 3, the authors could provide more detail on why introduction of some drugs would have a greater on drug consumption than others. For example switching from a coformulated branded drug to separate pill generic drugs resulting in a higher pill burden could lead to lower rates of a switch to the branded drug.

We added a paragraph within the methods sections: “Regional clinical pathways in Italy suggest the use of single tablet regimens, where possible. Therefore, in the definition of the therapy switch strategies, the availability of multiple generic pills had a limited effect on the rate of use of co-formulated tablet, to preserve the compliance of the patients.”

2nd to the last paragraph: "Generic drugs cost is estimated to be 80% of the branded equivalent’s cost in the first semester in which it enter the model and 50% of the branded equivalent’s cost in the following semesters” How do the authors arrive at these estimates? Please provide a reference or justification.

We changed the hypotheses presented, considering a 60% reduction of the cost of generic drugs compared to branded ones, leading to a cost for generic drugs equal to 40% of the branded ones. This was defined analyzing the percentage reduction of the three generic antiretroviral drugs already available in the Italian market, which had a mean reduction of price from the branded drug of 63%.

Minor Issues Not for Publication
The manuscript needs a review for language/grammar

We improved the readability of the paper with a revision by a British mother tongue expert.
Reviewer's report:
This analysis estimates the potential savings in Italy from switching to generic versions of antiretrovirals. I would suggest these major compulsory revisions to help with the interpretation of the results:

1. The current analysis is for the time period of 2013-2017. However since 2013-2014 is already in the past, it would be more appropriate to start the analysis in the current year, 2015 and to continue the analysis until 2019. This is the most interesting time interval, when a range of antiretrovirals become generic.

Following the suggestion of the reviewer, we updated the analysis, considering 2015-2019 time horizon

2. A new table should be included, showing the percentage of people taking each antiretroviral at the end of 2014, and then how these percentages are expected to change over time in the base case analysis.

We included a table showing patients distribution in the base case scenario and in the “new and generic drugs” scenario. Due to the number of therapies considered, we would suggest to add this table as supplementary material.

3. The use of Single Tablet Regimens versus individual drugs should be described in more detail. For example in 2018 when tenofovir, FTC and efavirenz are all available as generics, would all patients switch to the individual generic pills, or continue to take the single co-formulated tablet, which will still be patented?

We added a paragraph within the methods sections: “Regional clinical pathways in Italy suggest the use of single tablet regimens, where possible. Therefore, in the definition of the therapy switch strategies, the availability of multiple generic pills had a limited effect on the rate of use of co-formulated tablet, to preserve the compliance of the patients.”

We crosschecked the year in which tenofovir will be available as a generic drug in the Italian market, both through documents related to the Ministry of Health and through the company that produce the product. However no information were collected concerning the time horizon considered in the analysis. The use of TDF/FTC was also concerned by the future availability of TAF/FTC. According to the authors, due to the better profile in terms of reduced toxicity, TAF/FTC will be recommended by guidelines, discouraging the use of multiple drugs where possible. However, the assumption made by the author is that the cost of TAF/FTC will be the same of TDF/FTC and its rate of use will be equal to TDF/FTC.

4. There is a generic once daily version of nevirapine being developed which should be launched in 2016 in Europe. So generic nevirapine should be included in the analysis.

We added NVP 400 generic drug within the model, as suggested by the reviewer.

5. In the UK, generic antiretrovirals are already up to 90% cheaper than branded versions. The assumption of only 50% reduction in price seems too conservative. It should be clear where this assumption comes from.

We changed the hypotheses presented, considering a 60% reduction of the cost of generic drugs compared to branded ones, leading to a cost for generic drugs equal to 40% of the branded ones. This was defined analyzing the percentage reduction of the three generic antiretroviral drugs already available in the Italian market, which had a mean reduction of price from the branded drug of 63%.

6. Results should be presented more graphically, if possible. For example a graph showing the total cost of antiretrovirals in Italy in each year from 2015 to 2019, assuming no use of generics, versus full use of generics where possible could be included.

An image was added following the reviewer suggestion.

Discretionary revisions
There are other ways to save money in addition to switching to generics. For example, three randomised trials (GARDEL, OLE, SALT) have shown sustained efficacy after switching from triple therapy to PI/r + 3TC treatment. So for people currently taking TDF/FTC/PI/r, a switch to generic PI/r + 3TC (e.g. DRV/r + 3TC) in 2017 could save significant money, and also avoid the renal and bone toxicities of tenofovir.

The authors agree with the reviewer, however, considering the objective of the analysis we prefer not to introduce this interesting theme, which could be the topic of future analyses.
Reviewer's report:

Review: New Highly Active Antiretroviral drugs and generic drugs for the treatment of HIV infection: a budget impact analysis on the Italian National Health Service

Summary: The authors aim to assess the combined impact resulting from a) new lower cost generic entrants replacing patented medications, and b) new patented medications entering the market, on Italian national HIV-related expenditures.

Major compulsory revisions:

My main comment is that the methodology and data inputs are not transparent. I base this comment on the ISPOR good practice recommendations for budget impact models, which the authors themselves cite (#15). According to these recommendations, there are five key elements requiring data inputs to populate the analytic framework of a BIA:

1. Size and characteristics of affected population with and without the new intervention;
   a. OK, Provided by the authors – 86,370 in 2013 to 103,893 in 2017

2. Intervention mix with and without the new intervention;
   a. This is a major shortcoming of this analysis. The authors do not report the market share of drugs in the two scenarios. In fact, as far as I can infer from the very limited description of the methods, this analysis is not even based on market share assumptions, but takes the number of HIV-infected subjects on ART and multiplies it by a “rate of consumption”, which is then multiplied by a compliance estimate and then the apparently by the cost of drugs. It is absolutely not clear from the methods how the authors derive the cost estimates for the current scenario vs. the alternative scenario.
   b. The standard way of assessing the budget impact, in simplified terms, would include taking the market share of each drug, multiplied by the average cost of each drug to calculate the current scenario and then applying changes to market shares and changes to the cost structure to calculate the alternative scenario. The difference would then be the budget impact. However, it seems the authors deviate from this methodology in a way that is not transparent.

We added a table to show the percentage of patients distribution in the base case scenario and in the “new and generic drugs” scenario. Annual cost of each ART, calculated as explained in the methods, was multiplied by the number of patients assigned to each ART.

The total cost of each scenario was compared to the base case scenario to assess the budget impact.

3. Costs of current and new intervention mix;
   a. Another major shortcoming, the authors do not provide the drug costs of currently available medications anywhere in the manuscript. How can a paper based on a budget impact model not include drug costs anywhere? Furthermore, the assumption of a 20% decline in the first semester and a 50% decline in subsequent semesters associated with generic penetration is not referenced, where did this assumption come from? Branded drugs have gone generic in Italy in the past, what has been the historic experience, surely there must be literature or a dataset one could reference in this context.

The cost of each antiretroviral drug was taken from the Lombardy Region HIV/AIDS clinical pathway, as stated in the manuscript and available online:

Directorate General for Health of Lombardy Region D.d.g. 22 December 2014 - n. 12515 - Approvazione del documento avente ad oggetto “Percorso diagnostico terapeutico (PDT) del paziente affetto da malattia HIV/AIDS – anno 2105.


However, if preferred, we can add the table of the clinical pathway within the manuscript.

We changed the hypotheses presented, considering a 60% reduction of the cost of generic drugs compared to branded ones, leading to a cost for generic drugs equal to 40% of the branded ones. This was defined
analyzing the percentage reduction of the three generic antiretroviral drugs already available in the Italian market, which had a mean reduction of price from the branded drug of 63%.

4. Use and cost of other condition-related health-care services;
a. These are not reported either. I would assume that this analysis is based exclusively on the drug budget, but the authors should have made that clear in the methods.

The costs considered are those of ART drugs, as stated in lines 140 and 232.

5. Ranges and alternative values for sensitivity and scenario analyses
a. OK, Provided by authors, at least for select inputs, Table 1.

Minor compulsory revisions: 
1. The manuscript contains a number of grammatical inaccuracies (lines 29, 63, and many others) and could benefit from a through proof reading.

We improved the readability of the paper with a revision by a British mother tongue expert.

2. It is not clear what an “efficient” drug as stated in the conclusion is supposed to be.

We eliminated the word “efficient”.

3. The term “resource limited setting” is generally applied to resource limited countries, which are low-income and low-middle income countries as defined by the World Bank. A high-income industrialized country like Italy is certainly not on this list, so references to “resource limited settings” should be removed (although of course in economic terms every setting is technically resource limited).

We eliminated the term, as suggested by the reviewer.

4. Most of the introduction centers around how expensive HIV medications are in various European countries, but what I found was missing from this discussion was any reference to the value patients get in return. There is nothing wrong with expensive medications, as long they are associated with a significant social benefit. There was a study a few years ago that assessed social value of HIV therapies, which might be appropriate to cite in this context (Philipson, Tomas J., and Anupam B. Jena. "Who benefits from new medical technologies? Estimates of consumer and producer surpluses for HIV/AIDS drugs." Forum for Health Economics & Policy. Vol. 9. No. 2. 2006.)

We agree with the reviewer, however considering the objective of the analysis we don’t think this topic should be developed within the article.

5. The discussion is very thin, there is some reference to other published studies in this area, but the discussion does not address broader clinical, social, and economic implications of the findings.

Since the objective of the study presented is to assess the impact of generic and new antiretroviral drugs on the budget of the Italian National Health Service, the topics suggested by the reviewers could be appropriately addressed in future studies.

6. Furthermore, there is no reference in the discussion or introduction to support the statement that the generic and branded versions of the medications of interest are indeed bioequivalent. A quick pubmed search for bioequivalence of generic HIV medications found several published manuscripts indicating that although the pharmacokinetic exposure was similar, the generic version of stavudine, lamivudine, and nevirapine, did not meet the strict criteria for bioequivalence to the branded original. In how far these
findings are relevant to the Italian setting, I am not sure, but at the very least this finding should be discussed.

However the topic raised by the reviewer is of interest, considering the objective of the article we don’t think it would be appropriate to stress this topic within the article.