Reviewer's report

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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Reviewer: Andreas Kuznik

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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.

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.

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.

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.

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

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).

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.)

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.

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.

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests