Author's response to reviews

Title: Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence

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Author’s response to reviews: see over
Reviewer's report

Title: Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence

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Reviewer: dick menzies

Reviewer's report:

RE: Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence
First Author: Christine Currie

This modeling analysis compares seven different strategies for reducing burden of TB and HIV in Kenya. The most striking finding is that improving TB case detection rates or TB cure rates, particularly improving both, would have lowest cost and be most cost effective. Provision of anti-retroviral therapy (ART) would be very expensive although would provide substantial gains in terms of DALYs. Treatment of latent TB infection would have minimal benefits and would be very expensive.

These findings are reassuring in that they confirm the suspicion of many that using low cost AFB smears to diagnose TB patients, and low cost standard short course regimens to treat TB patients are by far the most cost-effective means to reduce the burden of TB in high TB and HIV prevalence setting.

Strengths of the study
1- Clearly the greatest strength is that this is a highly experienced team who have performed a number of economic and other modeling analyses in the past and have access to rich sources of data.
2- The authors made use of data gathered recently in Kenya regarding patient, family, and health system costs for diagnosis and treatment of active TB. The referenced study was carefully performed improving the precision of estimates of these costs.
3- The results are important and of interest in informing the current debate over priorities for public health spending in countries with high HIV and TB. The findings reinforce the importance of insuring that basic TB services AFB smear microscopy and standardized short-course therapy are not jeopardized by diversion of resources into provision of ART.

We found the reviewer's comments very helpful and have addressed all of them. This has improved the paper and we believe that it is now suitable for publication. The way in which we have addressed each comment is explained in the red text below, immediately after the relevant reviewer comment(s).

Major compulsory revisions:
1- I find the model rather opaque. I do not have ready access to the article references in which the model is described in greater detail, therefore more detailed description would be useful such as describing the rates of TB annually and the different HIV clinical stages and HIV uninfected. Or the authors could provide this as a supplement. We have now included a much fuller description of the model in the text, based on the description given in the original paper published in AIDS in 2003 (see pages 6-7). We have also included a new Figure (Figure 2) to illustrate the model.
2- It is unclear to me if they have explicitly modeled impact of these interventions on TB transmission. As I understand the paper, they do not appear to have done so. This limitation should be discussed more carefully in the discussion. We have revised the text to make it clear that the model does allow the impact of strategies on TB transmission to be considered. At the top of page 5 there is now text that reads "In a previous study[10], we used a dynamic model to compare the impact of a range of strategies on TB incidence and mortality in African countries with a high HIV prevalence. This model allows for the
effect of strategies on TB transmission to be captured." On page 6, we have also added text that reads "The TB model was designed so that the impact of strategies on TB transmission can be captured, and consists of two sub-models." (paragraph 2).

3. My biggest concern is in regard to the cost estimates; in particular the assumptions around the increased costs associated with increased case detection or increased treatment success. It is unclear why a 50% increase in costs is a reasonable assumption, might there not be some more substantial initial implementation costs in order to enhance either case finding of treatment success followed by recurring costs. I would have thought that they could incorporate some costs for initial DOTS implementation, taken from other countries such as China or India where DOTS expansion involved enormous initial spending for training and infrastructure in order to achieve increased case detection and treatment success. At minimum the costs should be varied more widely and some acknowledgement of a greater initial cost to step up these parameters on a national level should be included. These are all reasonable points. When the paper was initially written in mid-2004, the relevant data were limited. For example, while there were data on what India has spent on DOTS implementation as population coverage has expanded and case detection rates have improved, these data show that as rapid expansion has occurred, the average cost per patient treated has been stable (as reported in WHO’s annual TB report for 2005). For China, the available data are only from 2002 onwards, when China began submitting financial data to WHO. This is some time after DOTS implementation started in the early 1990s. Of particular importance, data have been lacking on the costs of increasing case detection once a country achieves 100% DOTS population coverage, which is the situation that applies in Kenya and many other high HIV prevalence African countries. This is why we had to make assumptions in the paper when it was originally written. Since the beginning of 2005, more relevant data have become available - through financial data that are now routinely submitted to WHO and that were published in the annual WHO TB control report for 2005, from GFATM funding proposals including two for Kenya, and from the plans and related analyses that have been done as part of the development of a second Global Plan to Stop TB (2006-2015) by the Stop TB Partnership during 2005. These data suggest that improving cure rates from their existing level to the target of 85% will roughly double the average cost per patient treated in Kenya and in Africa as a whole, and that improving the case detection rate will result in a two to four fold increase in the cost per new smear positive patient detected in Kenya and in Africa as a whole. We have revised the analyses to use these data, and the new means, uncertainty intervals and sources of data are shown in Table 1. We also considered the option of including a "fixed" cost for improvements to case detection and cure rates. However, since our results using the estimates of the factor by which average costs will increase when case detection and cure rates are improved were consistent with the total increase in the TB control budget for improvements to case detection and cure rates planned in Kenya (about US$11.5 million per year), we felt it was sufficient to report results using the average cost approach only. Nonetheless, in the discussion we have added some text stating that the average cost increase/fixed cost approach yield comparable results (p16). Cost of treatment of HIV related conditions and for ART are referenced as taken from a paper published in The Lancet. It would be useful to see the actual parameters from this paper that the authors used in this analysis. It would also be useful to see a greater variation in the costs for ART. Given the highly politicized debate over costs for ART at the present perhaps these costs could be varied more widely and some threshold analysis considered at which provision of ART might be cost saving if the annual cost for treatment were low enough. This is a second example of more data becoming available in 2005. We have revised the paper to use the latest set of unit cost estimates produced by UNAIDS in June 2005. These unit costs have been used in the UNAIDS estimates of the resources required for a comprehensive response to the HIV/AIDS epidemic in 135 countries, and were shared with us by the person responsible for doing the cost analyses related to HIV treatment, care and support (Juan Pablo Gutierrez, also the first author on the reference we previously quoted in the Lancet). The cost parameters are not officially published by UNAIDS because they do not publish country-specific cost estimates. Therefore, what we have done (and in line with the referee suggestion) is to use the range of values estimated for low income high HIV prevalence countries in Africa. Kenya is in the middle of the range in all instances. In this way, we have included wider variation for ART costs, as suggested. The upper and lower limit of the uncertainty distribution are the highest and lowest values estimated by UNAIDS for low income high HIV prevalence African countries. Rather than consider at what cost ART would be cost-saving, we have included a statement in the discussion of the cost per DALY gained by ART if drug costs were zero. We have done this because we believe that it is drug costs.
that are capable of falling lower than the level used in the analyses, but the lowest they can go is to zero cost. Other costs seem unlikely to fall, especially as they are based on a very decentralized and community-based model of care (as noted in the paper).

4- Drop-out rate for ART ranged only from 5% to 20%. This is extremely low for daily, presumably self-administered, therapy. This should be varied more widely, ie up to 50%. Also the authors should discuss the potential problems of drug resistance developing with self-administered therapy. Alternatively they could consider the costs of DOT for ART. We have used the range of 5% to 20% because this has been the range reported in practice to date. A recent paper, that has reviewed evidence regarding adherence to ART in Africa, is consistent with adherence rates being high, and in the range 80 to 95%. For this reason, we have maintained the analyses that consider drop out rates of 5% to 20%, and not included an analysis using a 50% drop out rate. We have added this very recent reference to the paper, to support the drop out rates used (Akileswaran et al, reference 22). We have also maintained the costs as estimated by UNAIDS, because these are the costs that have been estimated for the WHO/UNAIDS recommended approach to delivery of ART in the context of the “3 by 5” initiative.

Minor essential revisions:

5- The results are presented largely in Figure form rather than in Tables, this makes it seems somewhat harder to digest. A Table of the main results would be helpful. We have added three summary tables, one for the main set of results using a time frame of 20 years, and two further tables showing the same major results for 2 of the sensitivity analyses that we did (considering a timeframe of 10 years, and considering the strategies in the context of HIV prevalence being half the level assumed in our main set of analyses). These tables show the total costs, the incremental costs, the incremental effects, and the cost-effectiveness indicators (cost per DALY gained, cost per death averted, cost per TB case averted) for each of the strategies considered.

Minor discretionary revisions:

6- A useful reference the authors may wish to consider for TB progression in HIV states is a study by Wood and colleagues in South Africa published in The Journal of Acquired Immunodeficiency Syndrome 2000; 23: 75-80. We have retained the references used in our previous study, which were the references used when our model for TB progression among people with HIV was originally developed.

Dick Menzies

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare I have no competing interests