Author's response to reviews

Title: Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa

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Author's response to reviews: see over
Reviewer's report #1
Reviewer: Brian G Williams

General comment
This is a good paper that reaches important conclusions. In general the paper is well written but there are two important revisions that need to be considered and some questions of detail.

Major compulsory revisions
1. The WHO Guidelines have now been changed (reluctantly on the part of WHO) from starting ART at CD4 cell counts below 350/micro-litre to all those with a CD4 cell count below 500/micro-litre, all those with TB, Hep B, Hep C, under five, pregnant women and anyone in a "discordant relationship". My own calculations suggest that this would cover at least 90% of all HIV positive people in South African which therefore corresponds to immediate treatment in all but name. In spite of this South Africa is still sticking to 350/micro-litre although I understand that South Africa has agreed to adopt the new WHO guidelines in April 2014. I think that the comparison with what the authors call "Universal" is still valid as it will give added impetus for adopting the new guidelines as soon as possible. However, they need to reword their manuscript to reflect this.

Response: The reviewer discusses an important advancement in the definition of WHO guidelines for ART scale up, as well as the delay South Africa has in adopting these new guidelines. In fact, the most recently published recommendations from South Africa’s department of health (March 2013) are still following the CD4+ cutoff of 350 cells/microliter. We agree with the author that our paper’s findings could give new impetus to South Africa’s adoption of the updated guidelines. We have modified Paragraph 3 in the Background section to reflect this. The last sentence now reads:

“More recently, the guidelines have been expanded to include a broader population, although country-specific guidelines lag behind [13, 14]. Even in South Africa, where national guidelines support ART for more individuals than any resource-limited country, it is unclear when ART initiation would expand to those with higher CD4 cell counts.”

2. Second, the authors assume that PreP reduces transmission by 60% while treatment reduces transmission by 95%. Yet, in their Figure 2b, for example, PreP scale up to 100% averts almost as many infections as (about 3.8 million) as does ART (about 4.0 million). This seems unlikely or at least in need of an explanation.

Response: The reviewer brings up an interesting and important finding that deserves more discussion. In Figure 2b, we show that when implemented with Universal ART 100% General PrEP averts 3,800,000 infections. We also show, in the same figure and Additional file 1 Figure 2 that simply introducing Universal ART (offering the base case ART access of 10% to all infected individuals) offers incremental benefits versus Guidelines ART due to broader eligibility criteria (1,530,000 infections averted). Hence, a significant proportion of the infections averted by the portfolios of Universal ART and General PrEP can be attributed to the expansion of ART eligibility criteria, and PrEP averts at most an additional 2,270,000 infections when added to Universal ART. This observation highlights the importance of using a dynamic model that can explore a range of intervention portfolios and capture the effects of program overlap

We now make a note of this in section “Health Benefits of Scaling Up ART and PrEP”, when introducing Figure 2:
“Note that as indicated in Figure 2b, a 10% Universal ART program offers incremental benefits versus the status quo due to expanded ART eligibility criteria (1,530,000 infections averted); adding General PrEP averts at most an additional 2,270,000 infections.”

Minor essential revisions
1. The authors talk about “five new modalities”. I am not sure what the word "modality" means in this context but one of them is "vaccines" which have not yet been developed so this should be omitted.

Response: We agree with the reviewer that grouping vaccines along with other intervention that have already been implemented in practice might be misleading, so we have modified Paragraph 2 in the Background section to include only the other four interventions. It now reads:

“While many HIV programs in sub-Saharan Africa invested heavily in expanding ART coverage, scientific advances in recent years have resulted in four new HIV prevention interventions: male circumcision, topical microbicides, oral pre-exposure prophylaxis (PrEP), and ART for prevention [6-10].”

2. While I like the paper some of the figures are hard to interpret, the figure captions do not make it easy for the reader to interpret the information and the discussion of the figures in the text is not all clear. While the text mentions that what is plotted is "infections averted over 20 years" this needs to be said in the figure caption. In Figure 3 the colours and outlines of the various dots are not mentioned in the figure caption. The reader then has to go to Figure 1 to work out what they are and even in Figure 1 it is not immediately clear.

Response: We thank the reviewer for pointing out this important improvement to our paper. We fully agree that the figures and captions should be as clear as possible and we have revised them to make them clearer to read and interpret. For example, the caption for Figure 1a now reads:

“Figure 1a: Infections averted over 20 years with 100% scale up for single or combination programs: Guidelines ART (individuals with CD4 cell counts ≤ 350 cells/µl only), Universal ART (all HIV infected individuals), General Pre-exposure prophylaxis (general population), Focused Pre-exposure prophylaxis (individuals at high-risk of acquiring HIV). The bar colors indicate type of ART program, the bar outline indicates type of PrEP program. Bars 1, 2 show results of ART programs alone, 3,4 show results of PrEP programs alone, and bars 5-8 show results of pairwise combinations of ART and PrEP programs. ART strategies indicated by bar color: Guidelines - Red; Universal – Orange; Status quo – No color PrEP strategies indicated by bar outline: General - Solid line; Focused - Dashed line; Status quo – No line”

Reviewer's report #2
Reviewer: James G. Kahn

Reviewer's report:
This is a generally excellent assessment of the cost-effectiveness of PrEP and ART for HIV in South Africa. I like the modeling approach and the clarity of exposition in the narrative. I find the results (the cost-effectiveness of ART and PrEP general/focused, alone and in combination) credible and informative. This paper should make a very useful contribution to the literature in this area. Its findings are not unique, but provide important confirmation and added detail to existing work.
Response: Our model complements existing work and offers distinct contributions from previous papers in several ways. As indicated in a recent review by Gomez et al (now cited as [22] in our paper), our model is the only one to consider a planning horizon of 20 years. The longer time horizon allows us to incorporate long-term epidemiologic implications, including diminishing program returns and long-term program costs. At the same time, 20 years is not a time horizon that prevents us from making reasonable projections.

Another difference from the original cost-effectiveness study of PrEP (Walensky et al) is that we model incidence and epidemiologic outcomes dynamically, for the whole population including men and women. Our study is the only one to use dynamic compartmental simulation, an approach that is particularly suitable to evaluate the impact of scaling up PrEP and ART at the population level, thus informing country-level decision makers. We also are the only ones to consider a broad range of intervention portfolios and to model the effects of combinations of PrEP and ART at every scale (including Universal ART), which allows us to tease out incremental benefits and less-than-additive effects of overlapping programs.

My concerns have to do with presentation of results, and in particular the use of tables and figures, as well as making CE ratios incremental, temporal presentation, and costing the focusing of PrEP. I consider all of these reviews mandatory.

1. The labeling in the tables and figures is not intuitive, using letters and abbreviations that require footnotes which are, in turn, not entirely explanatory and clear. Table 2 (outcomes) is an example of this. I strongly recommend making each table and figure understandable on its own.

2. The figure legends are too brief. In my view, each figure legend should guide the interpretation of the figure, so that the reader can make sense of it without reference to the text.

Response for #1 and #2: We thank the reviewer for pointing out these important improvements to our paper. We fully agree that the figures, tables and captions should be as clear as possible and we have revised them to make them more straightforward. See response to R1’s Minor Comment #2 for an example of one of our revisions.

3. Cost-effectiveness ratios for different options are compared with the status quo. I believe that the more appropriate comparison is with the next least expensive option, i.e., stepwise incremental. Thus, for example, the cost-effectiveness of universal ART might be in comparison with guideline ART, indicating the added health benefit and cost of the incremental ART expansion.

Response: We agree. Presenting the results versus the next least expensive option is the sound and theoretically grounded way of presenting cost-effectiveness ratios. Indeed, throughout the paper this is our principal approach to presenting the findings. In the abstract, we chose to reference the strategies relative to the status quo because we explored the whole space of potential intervention combinations, and we wanted to avoid confusion. In the revised manuscript we include both absolute and incremental cost-effectiveness ratios in the abstract Results, where their inclusion improves transparency and precision. Our mention of PrEP cost effectiveness now reads: “General PrEP is costly and provides small benefits beyond ART scale-up ($13,300/QALY when added to 100% Universal ART).”
4. I couldn’t understand the following paragraph, perhaps because of the underlined portion which suggests that a “smaller program scale” leads to a “large proportion” of coverage, which seems to contradict the term “smaller scale”. Please clarify.

“Scaling up General PrEP alone to 100% while keeping ART at current recruitment levels would avert 63% of new infections over 20 years. Most of PrEP’s benefits are achieved with smaller scale General PrEP programs: increasing PrEP coverage from 50% to 100% in the general population for any given ART level averts only an additional 2%-7% of new infections. This is because a large proportion of uninfected individuals will start PrEP over the time horizon even with a smaller program scale, and the incremental benefits of an initially less aggressive program approach the benefits of a more aggressive program over time.”

Response: We have rephrased the paragraph to clarify the meaning of our comment. We define program scale as the rate of recruiting new individuals into the program. With a large enough rate of recruiting, more individuals will enter the program than those who leave, and the proportion of individuals who are in the program will steadily increase. The revised paragraph now includes the following text:

“Scaling up General PrEP alone to 100% while keeping ART at current recruitment levels would avert 63% of new infections over 20 years. Most of PrEP’s benefits are achieved with General PrEP programs with less aggressive recruitment rates: increasing PrEP recruitment rate from 50% to 100% in the general population for any given ART level averts only an additional 2%-7% of new infections. This is because a significant proportion of uninfected individuals will start PrEP over the time horizon even with a less aggressive program recruitment, and the incremental benefits of an initially less aggressive program approach the benefits of a more aggressive program over time.”

5. I’d really like to see results over time – costs and QALYs in particular. For example, the fact that universal ART looks attractive at 20 years is important, and consistent with past work. However, the time required to achieve the favorable results is unclear ... I strongly suspect initially unfavorable results, with steady improvements over time due to HIV infections averted. If the time horizon were extended to 30 or 40 years, there might even be net savings.

Response: The reviewer points out an important effect of planning horizon used to evaluate programs, which highlights the unique contribution our model brings. Indeed, when looking at the results for 10 years, Universal ART appears less favorable (while still cost effective), at $490/QALY gained versus status quo. Taking into account benefits and costs over 20 years, this cost is $310/QALY. Hence, Universal ART becomes more attractive if we consider the long-term impact, and the effects may become even stronger with longer horizons. We chose to use a 20 year time horizon since, unlike longer horizons, this timeframe is still considered relevant for practical decision making. We have incorporated a sentence in the discussion to highlight this important finding. Our discussion of Universal ART now includes:

“However, universal treatment is associated with a greater number of infections averted and a greater gain in QALYs for each unit investment in resources relative to the status quo, and the results get increasingly attractive as we consider longer planning horizons.”

6. Focused PrEP is attractive, if, as the authors note, it is “feasible”. However, as far as I can tell, there is no attempt to estimate the cost of efforts required to implement focused PrEP. I.e., identifying individuals at high risk, initially and over time. I suspect this is largely an unknown. If true, I recommend
wide sensitivity analyses on the cost of focused PrEP. How much added cost of focusing would put PrEP back into similar CE range as general PrEP?

Response: The reviewer is correct in identifying this important challenge in implementing Focused PrEP at a country level. The costs of finding and recruiting high risk individuals into the program is indeed unknown, so we have varied the cost of PrEP in sensitivity analyses. We found that Focused PrEP ceases to be cost saving at a yearly cost of $150, versus $80 in the base case. Focused PrEP cost as much as Universal ART per QALY ($310/QALY) at a PrEP annual cost of $260 per person. To be as expensive as General PrEP in the base case, Focused PrEP would have to cost $580 per person per year. These results indicate that Focused PrEP may still be an attractive option even if the costs to identify and target high risk individuals are $180 per person (the difference versus the $80 cost per person we used in the base case). The budget implications of such an additional cost would be significant, since total program costs for the first year alone would jump from $240 million to $780 million.

We have added this important insight to our Sensitivity analysis section, which now reads:

“The Focused PrEP strategy was no longer cost-saving for costs of PrEP above $150. This price increase may reflect additional costs to target high-risk individuals, improve adherence and monitor for adverse effects of PrEP. To be as cost effective as universal ART ($310/QALY), Focused PrEP annual cost would be $260 per person, and $580 to cost as much per QALY ($1,200/QALY) as General PrEP at $80 in the base case.”