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
January 27, 14

Dear Dr. Denyer,

We are pleased to submit a revision of our manuscript, "Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa" for additional review. We appreciate the detailed attention and helpful suggestions provided by Reviewer 2. The revision includes updated analyses and revised figures. We took great care to respond to the reviewer’s comments thoroughly, and the revised letter and manuscript contains point-by-point responses to the reviewer’s comments copied verbatim. We believe that the resulting manuscript is meaningfully stronger.

If we can provide any further useful information or revisions, please let us know. Thank you for your interest in our work.

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Reviewer’s report: The paper is improved. However, not quite there. In order & numbering of issues in my original review:

1. Please note that at least one prior paper on the cost-effectiveness of ART for prevention (but not PrEP) used a long time frame. This is Granich, Kahn, et al.  
This is a fair point, as the reviewer correctly points out that existing studies of ART cost effectiveness have used longer time frames; to the best of our knowledge, however, this has not been the case for PrEP. To give credit where credit is due, we now make note of this in the manuscript:

“One study estimating the cost-effectiveness of ART for prevention (without PrEP) uses a long time frames [23].”

2. The design / labeling of tables and figures remains unclear. Please get assistance of an editor or a test reader, to assure understandability. For example I took 30 minutes to understand Figure 3, and I’m an expert in this field. In addition the abstract is unclear and apparently contradictory. ** See uploaded file with further detail on these points **

This is a good suggestion, and we hope the new Figure 3 (+legend) is clearer. We consulted a colleague who is an HIV but not a cost-effectiveness expert for “informed layperson’s” advice. We modified the strategy markers; the modified figure legend is provided below (portions borrowed from the Reviewer’s suggestions), and can be found on page 24. We hope this will improve clarity, but we welcome additional suggestions from the editors or reviewer if the current version of the figure remains confusing.

“Figure 3: Cost-effectiveness (QALYs versus total costs over 20 years) of 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 dot shapes indicate type of ART program, the dot color indicates type of PrEP program.

ART strategies indicated by dot shape: Guidelines - triangle; Universal – diamond; Status quo – x mark

PrEP strategies indicated by dot color: General - black; Focused – gray. There is no PrEP in the status quo.”

Of note, we kept the two frontiers in the Figure, aware of the reviewer’s reservations in this respect. We kept this dual frontier because it reflects a fundamental insight of this paper regarding the importance of understanding the extent to which targeting PrEP based on risk is accurate and feasible. Collapsing the figure to reflect a single cost-effectiveness frontier, in our opinion, oversimplifies a critical point and may have policy implications about risk-targeted PrEP
that may not be grounded. This point is emphasized throughout the paper and abstract, and therefore we would welcome further suggestions to ensure that the point comes across clearly in the manuscript as well as the figures. A similar approach was used by Alistar et.al (http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000423) in a study where the main intervention (large scale implementation of methadone substitution therapy – denoted as “hi meth”) was potentially infeasible in practice due to political constraints. We include the figure from that paper below, for illustrative purposes.

We address the reviewer’s concerns about the abstract and the presentation of the findings below.

3. The results are still not stepwise incremental, e.g., in the abstract. That is, the authors say that the new abstract presents both vs. the status quo (which I believe is misleading) and incremental, but in fact for ART it presents only vs. status quo.

We have rephrased the abstract to discuss the incremental costs and benefits of strategies. It now reads:

“Scaling up ART to 50% of eligible individuals averts 1,513,000 infections over 20 years (Guidelines) and 3,591,000 infections (Universal). Universal ART is the most cost-effective strategy at any scale ($160-$220/QALY versus comparable scale Guidelines ART expansion). General PrEP is costly and provides limited benefits beyond ART scale-up ($7,680/QALY to add 100% PrEP to 50% Universal ART). Cost-effectiveness of General PrEP becomes less favorable when ART is widely given ($12,640/QALY gained when added to 100% Universal ART). If feasible, Focused PrEP is cost saving or highly cost effective versus status quo and when added to ART strategies.”

4. Rewrite of PrEP scale paragraph is now clear.

Thank you.
5. Adding the phrase "and the results get increasingly attractive as we consider longer planning horizons" is not responsive to my suggestion. I feel strongly that policy makers will want to understand how the economic results evolve over time, since they may not want to base policies only on such a long horizon. I think the paper will be more powerful with a figure showing year-by-year results. I would think this is fairly easier to generate.

We agree with the reviewer and we now provide findings from a 10-year projection in the discussion on page 14.

“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. 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.”

6) Focused PrEP cost - well-addressed.