Response to Reviewers' Comments

Re: EPIDEMICS-D-21-00134

Title: Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review

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1 Reviewer #1

This paper by Knight and colleagues reviews mathematical models of the impact of antiretroviral treatment (ART) on HIV incidence. A particular focus is on differences between models in terms of how they represent heterogeneity in HIV risk, and how this heterogeneity influences the predicted impact of ART on HIV incidence. The review is thorough and clearly presented.

> We thank the reviewer for their comment.

1.1 Major comments

1.1.1 A limitation of this review, which the authors acknowledge, is that it is essentially an ecological analysis. Although there is an association between models allowing for heterogeneity in risk behaviour and models predicting smaller ART impacts on HIV incidence, this finding doesn't necessarily prove that heterogeneity in risk behaviour determines the extent of the ART impact. There are many possible confounders and other variables that influence the extent of the modelled reductions in HIV incidence, as the authors note. Would it not make more sense to use a meta-regression approach to isolate the effect of the heterogeneity assumptions, controlling for the confounding factors? Although this wouldn't completely get around the causality conundrum, it would be better than the current approach, which is effectively relying on univariable rather than multivariable analysis.

> We agree with that the paper could be strengthened with a regression analysis, and have revised as suggested. We describe our analysis as a "multivariate regression", and not a "meta-regression", as we did not pool uncertainty estimates. Confidence intervals were only given for 6% incidence reduction (IR) data points, and 33% cumulative infections averted (CIA) data points, each data point representing the outcome (IR or CIA) reported for a unique study, scenario, and time-horizon. So, we did not attempt to integrate these confidence intervals in the regression as in a typical meta-regression.
>
> The variables included in the regression are given in Table 3 (formerly C.1), including the following possible confounders of heterogeneity factors: time horizon for outcome evaluation, HIV prevalence at time of ART scale-up, relative rate of HIV transmission of ART, and CD4 threshold for ART initiation in the scale-up scenario. Due to missingness (% missing data points for IR & CIA, respectively),

we omitted the variables: HIV incidence trend (19% & 53% missing), and ART coverage target (77% & 23% missing). More details about the regression are given in 1.1.2.

1.1.2 A related concern is that the tests for statistically significant differences in the univariable analysis appear problematic. When you use the Kruskal-Wallis test you are assuming independence of observations. But here the observations are not statistically independent of one another - in many cases multiple observations are being taken from the same study (and there is likely to be a high degree of within-study correlation). By not taking into account the within-study correlation I think you exaggerate the significance of the differences between model types. That might explain some of the odd results in Table C1 (for example a statistically significant positive relationship between HCT behaviour change and the incidence reduction, but a significant negative relationship between HCT behaviour change and the cumulative % of infections averted). If you use a meta-regression approach, you should be able to control for the within-study correlation.

To account for clustering of the data points by study, we used generalized estimating equations to fit the regression model (specifically, the `geeglm` model from the `geepack` packge in R). This semi-parametric model allows estimation of population-averaged effects of each factor on the outcome, while controlling for within-study correlation of outcomes as a nuisance. We assume independence (`corstr='independence'`) of outcomes within each cluster (study) because it is more robust for small / imbalanced data such as ours; this assumption would only affect the standard errors, not the point estimates of effects.

The regression model is described in Section 2.3.3 (Methods), while the adjusted effect estimates are added to Table 3 (formerly C.1), and key findings are highlighted in Section 3.3 (Results). Figures 2 and C.20 also gives a forest plots of effect estimates.

The key findings of the review have also been revised in light of the regression results: We found that heterogenetiy (defined by activity groups with or without key populations) acts through risk group turnover and cascade differences between groups. That is, across models, inclusion/exclusion of risk heterogeneity was not sufficient on its own to be associated with ART prevention impact. But if risk heterogenetiy included turnover and/or differential cascade, then risk heterogeneity was associated with ART prevention impact. The results in section 3.3 and the discussion have been revised substantially in light of these findings.

1.1.3 Although the authors explain why modelling key populations might influence the predicted impact of ART on HIV incidence, I think the introduction would be strengthened if they also mentioned the literature that covers heterogeneity more broadly – and the role that heterogeneity plays in determining intervention impact. For example, Nagelkerke et al (2007, BMC Infectious Diseases, 7:16) showed that the modelled impact of male circumcision on HIV incidence was much greater when assuming no heterogeneity in risk behaviour, Johnson et al (2012, Journal of the Royal Society Interface, 9:1544–54) showed that the modelled impact of condoms and ART was strongly correlated with the heterogeneity in risk behaviour, and Hontelez et al (2013, PLoS Medicine, 10:e1001534) showed that allowing for heterogeneity reduced the predicted impact of ART on HIV incidence. Key populations are one component of the heterogeneity–impact relationship, but the introduction currently reads as if they are the only determinant of the relationship.

> In addition to a broader description of populations with differential ART cascade (see 1.1.5), the following has been added to the beginning of the last paragraph in the introduction: "*Risk heterogeneity, defined by various factors affecting acquisition and onward transmission risk, is a well-established determinant of epidemic persistence and controllability with a basis in the modelling literature [Anderson1986, Boily1997]. Model comparison studies by Hontelez et al (2013) and Rozhnova et al (2016) found that projected prevention impacts of ART scale-up were smaller with greater heterogeneity.*"

1.1.4 Given that the results from Table C1 are so central to the overall conclusion of the paper (and are referred to in the abstract), it seems strange to put this table in the supplementary materials. I think it would be more appropriate to include this table in the main text of the article.

> We have updated the table to include the results of the regression analysis and moved the table into the main text. We moved the map (formerly Figure 2) to the appendix due to the limit of 5 figures and tables in the main text.

1.1.5 The third paragraph of the Introduction mentions possible inequalities in uptake of HIV testing and ART as an explanation for the lower-than-expected impact of UTT, and mentions a number of sub-populations that might be disadvantaged. But the authors fail to mention heterosexual men. There is much evidence of heterosexual men being at a disadvantage (in terms of HIV testing and ART uptake) and they also contribute more to transmission than heterosexual women, so why are they not mentioned here? Similarly in

the second and third paragraphs of the discussion the authors criticize modelling studies that don't consider key population dynamics, but they don't mention the challenges around engaging heterosexual men (and the problem that many models don't consider differences between men and women in ART coverage). The poor uptake of HIV testing and ART in heterosexual men is really the Achilles heel in the 'treatment as prevention' strategy in Africa, yet this issue is frequently ignored in the literature. I feel the authors could have drawn more attention to this issue throughout the paper, rather than focusing narrowly on the traditionally defined key populations.

> We have updated the introduction to mention heterosexual men: "*Populations experiencing barriers to viral suppression under UTT may be at highest risk for acquisition and onward transmission, including key populations such as women and men engaged in sex work, and men who have sex with men [Hakim2018, Nyato2019]. Data suggest other sub-populations, including youth and men who have sex with women, may also experience barriers to engagement in ART care [Green2020, Quinn2019] that could undermine treatment as prevention.*" Additionally, the "sex/gender" stratification variable for objective 3 has been updated to distinguish between models that do and do not consider lower cascade among men, with findings discussed in section 3.3. Note that we refer to the variable as "sex/gender", and not sex as a biological variable, because we are examining in the context of engagement in care (gender) and also transmission probability (sex as a biological variable).

1.1.6 It was not clear why the authors excluded individual-based approaches from this review. Although people tend to use the terms 'compartmental models' and 'deterministic models' interchangeably, some would argue the terms mean slightly different things (see Garnett, STIs, 2002, 78:7-12). The point is that it's possible for an individual-based model to be 'compartmental' in the sense that it works with categorical variables rather than continuously-defined variables. In such cases one could argue for including an individual-based model in the review, since its compartments/categories can be classified in the same way as a deterministic model. But even when key variables are defined on a continuous scale it's not clear why you would want to exclude the individual-based model from the review.

> We agree with the reviewer that individual-based models represent another important source of model-based evidence for quantifying ART prevention impacts, for which it is worth examining the various representations of heterogeneity, and their potential association with projected impacts. How-

> ever, as the reviewer suggests, we feel that it would be difficult to define criteria to include some but not all individual-based models, for example, on the basis that they include some compartmental-like stratification(s). Then, or if including all individual-based models, it would become unweildly to simultaneously compare both continuous and discrete representations of heterogeneity, such as population stratifications in compartmental models versus continuous sampling distributions for parameter values in individual-based models. The additional complexity of modelling concurrent partnerships as well would be challenging to synthesize well within the available space. We would look forward to conducting or supporting a complementary review focused specifically on individual-based models.

1.2 Minor comments

1.2.1 Page 6: I didn't understand this sentence: "Studies in Dataset B specifically examined scale-up of ART coverage alone (versus combination intervention) for the whole population (versus ART prioritized to subgroups)". The authors seem to be referring to multiple different comparisons in the same sentence. Perhaps it would help to rewrite as two sentences, focusing on the primary comparison of interest in the first sentence.

> We have clarified the sentence as follows: "*Studies in Dataset B met three additional criteria: 1) examined scale-up of ART coverage alone (versus combination intervention); 2) examined ART intervention for the whole population (versus ART prioritized to subgroups); and 3) reported HIV incidence reduction and/or cumulative HIV infections averted relative to a base-case scenario reflecting status quo.*"

1.2.2 Page 17: "Our ecological analysis also suggested that the anticipated ART prevention impacts from homogeneous models may be achievable in the context of risk heterogeneity if testing/treatment resources are prioritized to higher risk groups." I didn't follow this - what is this based on? The comparison of the 21% vs 10% on p. 15? If so, aren't the numbers too small to suggest a statistically significant difference? (See my earlier comment on testing for significant differences.)

> In the revised results and discussion following the regression analysis results, this sentence has been removed. The role of cascade differences as a possible determinant of ART prevention impacts is explored in the third paragraph of the discussion.

1.2.3 I felt there could have been more explanation for some of the unexpected findings in Table C1. As noted earlier, some of these odd findings might just be due to inappropriate statistical tests.

> In the regression analysis, adjusted factor effects appear to be more consistent with expected findings. Additionally, since the main factors of interest were those related to risk heterogeneity, we did not seek to explore or explain all covariate effects from the model, as per best practices in analyses of secondary data when the focus is on the primary exposure variables of interest — i.e. doing so could lead "table 2 fallacy". Finally, we added the following to the limitations paragraph: "*Third, we did not extract whether models were calibrated, and if so, which parameters were fixed vs fitted. If certain parameters were fitted, it could explain some counterintuitive effect estimates. For example, modelling increased infectiousness in late-stage HIV reduced ART prevention impacts. However, in most studies, newly ART-eligible patients via scale-up had earlier stage HIV; therefore, such patients would have lower modelled infectiousness than late-stage HIV, and lower infectiousness than in a model with uniform infectiousness fitted to the same data. A similar mechanism could explain increased ART prevention impacts when including acute infection.*"

1.2.4 The references in the supplementary materials are incorrectly formatted. Often they give the second initial of the author but not the first initial. For example, L. Korenromp (reference 62) should be E.L. Korenromp, and J. Abu-Raddad (reference 56) should be L.J. Abu-Raddad.

> Thank you for catching these errors. The references have been thoroughly checked and should now be correct.

2 Reviewer #2

Knight et al. present a systematic scoping review addressing the impact of risk heterogeneity representation on the estimated impact of antiretroviral therapy to reduce HIV transmission in sub-Saharan Africa. They find a range of risk heterogeneity model paramaterisation, in turn leading to substantial variation in the estimated reduction of HIV incidence/new infections attributable to ART. This represents a significant consolidation exercise and represents a timely and valuable addition to the literature as interest in risk heterogeneity in sub-Saharan Africa, including representation of key populations, increases.

> We thank the reviewer for their comment.

2.1 Major Comments

2.1.1 It's not immediately clear to me what the key recommendation is that flows from Figure 3. If I have a model with the base case (no risk heterogeneity), which compartments or dynamics should I add first better to represent the true epidemic?

> As described above in 1.1.2 in response to Reviewer 1 suggestions, the results section 3.3 and discussion have been substantially revised in light of more precise findings. The revised discussion now concludes with the following recommendations which we hope are more clear: "*In conclusion, model-based evidence of ART prevention impacts could likely be improved by: 1) consistenly including risk group turnover, as a determinant of inferred risk heterogeneity during model calibration, and to reflect challenges to maintaining ART coverage among risk groups with high turnover; 2) integrating data on differences in ART cascade between sexual risk groups, to reflect services as delivered on the ground; and 3) capturing heterogenetiy in risks in the context of key populations, to reflect intersections of transmission risk and barriers to HIV services that may undermine the prevention benefits of ART.*"

2.1.2 Further discussion of the headline finding would be welcome – that the omission of key populations but the inclusion of risk heterogeneity in the generalised population brings about the smallest declines in new HIV infections is notable. Where possible – interrogating which dynamics are most important in the discrepancy between 'Activity (no KP)' and the other three model scenarios would be of interest.

> In the new regression analysis, there is little difference in estimated effect between "Activity (no KP)" and "KP (same)", except for IR for "KP (same)", which had wide confidence interval based on only 5 scenario time horizons. This suggests that when the ART coverage is assumed to be the same between risk-groups, then the inclusion/exclusion of KP may not have as much influence on the outcome (prevention impact of ART). However, we note this interpretation with caution given the small number of scenarios available for this analyses.

2.1.3 Please elaborate on and support Figure C.11 – it's not immediately clear to me that 'the pattern of incidence reduction versus modelled heterogeneity was similar to the pattern of infections averted versus modelled heterogeneity". Recognising that these data do not stem from the same studies, it is noted that in Table C.1 the incidence reduction increases 2fold between no risk heterogeneity and activity (no KP), whilst averted infections decreases ~4 fold. This would appear to be a key difference?

> As noted above (2.1.2), the adjusted effect estimates for the "Risk Stratification & Cascade Differences" variable are now more consistent across both outcomes (incidence reduction and cumulative infections averted). We suggest that differences in unadjusted estimates were likely due to confounding by unaccounted factors, and random chance due to the small number of scenarios time horizons for some factor levels (e.g. 5 and 1 for "KP (same)" and "KP (priority)" incidence reduction data).

2.1.4 As HIV prevalence is linked to epidemic type, it's interesting that ART prevention impacts were larger with lower HIV prevalence. As the lower prevalence epidemics in West Africa are driven by KPs/more so than the epidemics in ESA, I assume that modelling studies in West Africa are more likely to be KP-disaggregated. However, you have shown that KP-disaggregated models estimate smaller ART prevention impacts. Could this be explored further?

> As hypothesized by the reviewer, the regression analysis reverses the estimated influence of HIV prevalence on ART prevention impacts: from larger impact with lower prevalence (43 vs 22 %IR, 26 vs 18 %CIA), to smaller impact with lower prevalence (-9 %IR, -9 %CIA).

2.1.5 Whilst recognising this is a scoping review, some more discussion on the impact of these findings for the global HIV response would be welcome. As noted in the discussion, modelled estimates "did not always reflect the available data". The key population estimates (and subsequent estimates of averted HIV transmission) are reliant on weak data and some informed comment on how these results should be used would be good.

> The key messages of the review and contextualization in the global HIV response are now hopefully more clear in the revised discussion (see 2.1.1). We additionally note possible priority areas for data collection such as: "*These findings suggest that turnover is important, and as such, models would benefit from surveys, cohorts, and repeated population size estimates that can provide data on individual-level trajectories of*

> *sexual risk, such as duration in sex work*" … "*Improved modelling and prioritization of sevices designed to reach key populations will rely on continued investment in community-led data collection for hard-to-reach populations*" … "*With the growth of data collected about communities most affected by HIV, there are opportunities to more consistenly capture data-driven heterogenetity in risks and intervention access among key populations in transmission models*".

2.2 Minor Comments

2.2.1 Figure 2: I would prefer HIV prevalence over PLHIV as the chloropleth.

> We have revised the figure to use HIV prevalence as the country colour.

2.2.2 Do any studies address the age distribution of key populations? This would be useful to include.

> TBD

2.2.3 Were transgender people or prisoners included in any studies?

> We added transgender people and prisoners to the key populations considered in the review, using the following definitions: "*Any activity group(s) described by the authors as transgender*" and "*Any activity group(s) described by the authors as prisoners*". Sections 2.3.1 (Methods), 3.1.1 (Results, including Table 2), and B.2.1 (Appendix: Definitions) in the manuscript were each updated accordingly.

2.2.4 I find the bubble plots difficult to interpret. The bubbles are often similarly sized, I'm not sure the extra information adds to the results and crowds the plot. Perhaps grouped bar charts or grouped box plots would be easier to read - particularly for Figure 3.

> We have revised to use boxplots, stratified by 10-year intervals of time since intervention, and categorizing previously continuous variables (HIV prevalence, ART coverage target, and relative infectiousness on ART).

2.2.5 Consider inserting Table C.1 into the main text

> We have moved the table into the main text (see 1.1.4).

2.2.6 Consider a sensitivity analysis of the main findings without South African data

> We explored the feasibility of this analysis. However, only 19 (IR) and 58 (CIA) data points were available without the South African data, leading to rank defficiency in the model, and thus the parameters could not be estimated without changing which parameters were included in the model.