Author’s response to reviews

Title: Decline in reported AIDS cases in Brazil after implementation of the Test and Treat Initiative

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Peer re-review, Mendes Pereira-GF et al., Decline in reported AIDS cases in Brazil after implementation of the Test and Treat Initiative, for BMC Inf. Dis., August 2018

GENERAL COMMENTS:
The authors have addressed all my comments, and the analysis and manuscript have improved.

Response: Thanks a lot for your review that has substantially improved the manuscript. Should you have additional comments or questions, we are happy to address them.

I have two major comments still:

1. The key revised results (Results sub-section: Changes in the AIDS detection…) look internally inconsistent between the numbers and rates shown in Figure 1, and the statistics presented in the results text. Specifically, with an AIDS detection rate over 2007-2014 averaging 20.45 and in 2015 7.70, the decrease between these periods can mathematically not be only 2.0% -- rather this is a 62% decline. Similarly, for mortality, the decline from 2.32 to 0.49 is 79%, not 8%.

I presume the 2.0% means an average ANNUAL decline? I wonder over 2007-2014, or over 2007-2015 averaged? I suggest to rephrase this paragraph as follows:

The AIDS detection rate … was 20.45 … and was 7.70, a 62% decline. In segmented Poisson regression, the decline over 2007-2014 was ?2.0%? annually (i.e. an odds ratio for annual decline of 0.98, 95% CI 0.98-1.0), and the predicted AIDS detection rate in 2015 absent Test and Treat in 2015 would have been ?e.g. 19.8? Thus the estimated drop in 2015 (adjusted for the pre-2015 trend) was ? e.g. 60%?.
The mortality rate ... was 2.32 before ... and 0.49 after T&T, a crude 79% decline. In segmented Poisson regression, the decline over 2007-2014 was 8.0% annually (i.e. an odds ratio for annual decline of 0.92, 95% CI 0.91-0.95), and the predicted AIDS detection rate in 2015 absent Test and Treat in 2015 would have been e.g. 2.1? Thus the estimated drop in 2015 (adjusted for the pre-2015 trend) was e.g. 73%?

This analysis could be visually clarified in Figure 1, by adding lines showing the regression-estimated trend, based on the 2007-2014 observed data but extended into 2015 – so one visually sees the prediction for 2015 and how much higher that is than the observed case or death rate in 2015.

Please also rewrite the Abstract accordingly – focusing on the estimated drop in 2015, relative to prediction from 2007-2014 trend.

Response: Thanks for this comment. The results and abstract have been rewritten and clarified.

2. I believe the paper would be strengthened if the data added in Supplemental Table 1 were moved into the main Results. To make space for this, the authors could consider to drop or condense results about the distribution of reported AIDS cases by age (Table 2) and by mode of transmission/infection (Figure 2) – which are really secondary analyses (of overall trends throughout 20108-2015 without analysis or evidence of interruption at 2015), that do not influence the interpretation of the overall key results about the recent interruption in the time trend in total AIDS cases.

Specifically, I see that the trends in the indicators presented in Supplemental Table 1, which complement AIDS diagnoses and deaths as additional key indicators in the cascade of HIV care, support and explain the drop in AIDS cases and AIDS deaths in 2015, and this deserves illustration and mentioning in the main results:

** The trend in number of rapid tests (increasing, with acceleration from 2012 onwards), numbers of new HIV diagnoses (increasing, with acceleration from 2013), and number of PLWH on ART (increasing, reflecting improved survival, with acceleration of the increase from 2013) and median CD4 count at ART enrolment (increasing, with acceleration of the increase from 2013) support this very well.

Response: Thanks for this comment. Table 2 and Figure 2 have been removed along with the corresponding narrative results. Supplemental table 1 with key indicators related to the cascade of HIV care has been moved to results and narrative results have been added. Also these variables are mentioned in methods, section data collection. Changes in the corresponding text of the discussion have been made.

Specific comments:
ABSTRACT, Conclusions: In my view the main conclusions should be about the overall drop in AIDS case reports, and its explanation based on the scale-up of HIV testing and resulting progress in detecting and enrolling HIV/AIDS patients into care and ART at earlier clinical stages – all this is evidenced in the Supplemental Table 1. This could be summarized in the abstract using the summary paragraph I inserted above **, about trends of increase and years of acceleration in these increases in those supplementary indicators.
Response: Thanks for this suggestion. The conclusions in the abstract and in the body of the manuscript have been modified. In my view, trends in modes of transmission are less relevant and may be omitted from the conclusion (in Abstract, and in main text).

Response: Trends in modes of transmission have been removed from the conclusions (in the abstract and in main text).

Last sentence: Suggest to rephrase as something like: ‘This evaluation of the effect of Test and Treat on AIDS diagnoses and mortality remains to be repeated and strengthened with forthcoming additional years of data.’

Response: Thanks for your suggestion. The sentence has been rephrased.

METHODS:

Last paragraph: Missing here is an explanation or rather justification (based on key policy and program implementation mile-stones and years) of, why you chose 2015 as the year of interruption. This is presented in the Discussion, but it could be summarized here.

Response: In the last paragraph of the methods section, a summary of the explanation of why 2015 was chosen as year of the interruption has been added based on key policy implementation years.

RESULTS:

Sub-section ‘Changes in the AIDS detection’:
The mortality rates shown I understand are AIDS-attributed deaths (as stated in Methods, last paragraph), not all-cause mortality rates in the overall (HIV+ and HIV-) adult population. Please clarify and make this consistent throughout the manuscript, tables and figure legends.

Response: The correct term is AIDS-attributed deaths, and this has been corrected throughout the manuscript, tables and legends.

Paragraph ‘The results of the logistic regression analysis…’: This variant or repetition of the key result of preceding section ‘Changes in the AIDS detection’ (there for all cases, here for the subset of heterosexuals) I think adds little, it could be dropped. However if you decide to keep it, then please rephrase and correct the statements about 2007-2014 average annual decline and the 2015 drop in heterosexual AIDS cases relative to the 2015 prediction from the 2007-2014 decline, as suggested above for all AIDS cases combined.

Response: Thanks for this comment. The results of the logistic analysis have been dropped form the results section both in the abstract and in the manuscript. The methods of the logistic regression have also been dropped from the statistical analysis section.

More generally, please choose a generic structure for the key results – either M+F combined, or M & F separately. Then do both Figure 1 and the key analysis (the interrupted trend regression, and 2nd Results paragraph) in that structure right away.

Consider to split Figure 1, into:
a) AIDS case reporting rate  
b) AIDS mortality  
… with in each of these 2 panels:  
- Dots (NOT connected by lines) representing the observed data  
- Lines representing the regression trend through these.  

Responses: The tables and figures are by sex. We believe it is important to provide the overall results and the overall estimates (M+F combined) has been left only in the narrative text not to burden the tables and figures. Figure 1 has been split in two, one with the AIDS case reporting rate and one with AIDS mortality. Dots now represent the observed data. The results of the regression analysis are presented in the text.  

DISCUSSION:  

The discussion repeats some of the Introduction, and contains much that rather belongs in an introduction than in a Discussion. Please restructure, remove overlap, and focus the discussion on interpretation of results. See specific suggestions below.  

Response: Thanks for this comments on the discussion. We have addressed them and we believe now the discussion has improved.  

‘Adopt of the T&T in Dec. 2013 and its subsequent implementation’ – move to the Methods paragraph stating 2015 as the interruption year for the interrupted trend regression.  

Response: This text has been moved to the methods as suggested.  

‘TasP is likely the major driver’: Effects of TaSP/ART on HIV transmission are beyond the scope, since you analyzed only outcomes of morbidity and mortality (AIDS cases and mortality) and not HIV incidence estimates. It is OK to still mention transmission/infectivity/prevention effects, but I would put those only after the key, immediate and chronologically first result of reducing AIDS morbidity and mortality.  

Response: The sentences related to HIV transmission, prevention, population level have been removed to avoid going beyond the scope of the study because we focused on morbidity and mortality.  

‘At the population level, expanded ART’: Qualify this as ‘in Canada’.  

Response: This sentence has been removed to avoid going beyond the scope of the study as we only analyzed morbidity and mortality.  

‘The proportion of patients with an HIV diagnosis increased from 77%’: 77% of what? Also note that un-diagnosed (prevalent or incident or estimated) HIV cases could hardly be called ‘patients’ – if that is what you mean, consider to rephrase as the proportion of PLWH, or of estimated new incident HIV cases.  

44% in 2012 and 55% in 2015: % of what?  
& Since which year, e.g. 2014 or …?  

Response: These sentences have now been rephrased and there is information in the results section and
some, more narrative, in the discussion.

‘5 separate PrEP demonstration projects’: I would add here up front that these were small-scale projects.

Response: It has now been stated that these projects were small-scale.

‘To accelerate effects towards…’ until ‘the health system [24]’: Much of this would fit logically in the Introduction – and does not need repetition in the Discussion.

Response: Thanks for this comment. This text has been moved now to the introduction.

‘In men, except for the final year, there was an increasing trend…’: Suggest to rephrase as ‘except for the final year’ as ‘over 2007-2013’.

Response: Thanks for this comment. The sentence has been rephrased.

‘… there was a significant trend among homosexual…’: Increase in what: diagnosed AIDS cases? Or the number (c.q. population size) of MSM?

Response: The increase was of diagnosed AIDS cases. This has been clarified in this version.

‘In contrast, AIDS trends in IDUs…’: Suggest to rephrase as ‘AIDS cases’.

Response: The sentence has been rephrased.

‘The association of crack with casual sex work and homelessness might contribute to the high proportion’: Suggest to rephrase proportion as ‘contribute to the persistently high share of IDU in AIDS cases’. Or drop the sentence.

Response: The sentence has been dropped.

‘The segmented Poisson regression was not adjusted by time-varying confounders’: I question if this is really a limitation. Increasing CD4 counts as ART enrolment is an intermediate variable in explaining the drop in mortality – so if the analysis adjusted for that, its result would understate the real progress and impact made, through advancing AIDS detection and ART to PLWH with higher CD4 counts, on mortality.

Response: Thanks for this comment. We are in agreement and the sentence has been dropped.

‘Furthermore, the mode of HIV transmission had a high proportion of missing values in some variables, such as IDU’: What was missing? Do you mean that some of the AIDS diagnoses had no mode-of-transmission category assigned? If so, then consider to add in that (supplementary) analysis a category ‘Mode of transmission unknown’.

Response: The proportion of missing (category unknown) in variables related to mode of transmission is very low and therefore this sentence has been removed.

CONCLUSION:
Suggest to summarize here again the key time points, e.g.’… related to the ART explanation … initiative since December 2013.

Response: The key time point has been added to the text.

Drop: ‘Shifts were observed in the distribution…’

Response: This sentence has been dropped.

‘A major challenge… expand periodic HIV testing, specifically targeting the most-at-risk populations’: This discussion of programmatic implications and recommendations is very important -- but first mentioned here -- so move this out of the conclusion, to a dedicated paragraph higher up in the Discussion.

Response: This paragraph has been move to the discussion section.

SUPPLEMENTAL TABLE 1:
Great, important data to support the overall analysis. Move into main results.
Standardize all numbers in the table using a standardized thousands separator (e.g. comma is conventional in English).

Response: Thanks for this comment. The table has been moved to results. Numbers in the table have been standardized using comma as a separator.

FIGURE 2: Could be dropped, or downgraded to an annex. If you keep it, make the patterns better distinguishable, with more contrast between light/empty series and dark/fully patterned.

Response: Thanks for this comment. Figure 2 has been dropped.