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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Version: 1 Date: 14 Aug 2018

Author’s response to reviews:

Technical Comments:

1) On the title page, please include the email addresses of all co-authors.

Response: the email of all co-authors have been included in this reviewed version.

2) The abstract should be subdivided into the following headings:
   - Background
   - Methods
   - Results
   - Conclusions

Response: The abstract has been subdivided in the suggested headings.

3) The main manuscript should be subdivided into the following headings:
   - Background
   - Methods
   - Results
   - Discussion
   - Conclusions

Response: The main manuscript has been subdivided in the suggested headings.

4) The "Conclusions" should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.
Conclusions have been rephrased to state clearly main conclusions, both in the abstract and in the discussion.

5) Please move the Abbreviations to after the Conclusions.
Response: The abbreviations have been moved to after the Conclusions.

6) Pleases move the "Declarations" section to after the Abbreviations.
Response: The "Declarations" section has been moved after the Abbreviations and has been reordered to follow the structure suggested by the journal.

7) For all research involving human subjects, informed consent to participate in the study should be obtained from participants or their parent or legal guardian in the case of children under 16. Under the heading "Ethics and consent to participate" please add the statement that you included in the methods: "In Brazil, according to law CFM n°1.865/96, authorization or consent from parents or responsible person is not needed to perform an HIV test in individuals after 12 years of age if the test is voluntary and consent is provided by the adolescent, provided that the adolescent has the capacity to evaluate their problem and take actions accordingly."
Response: The statement included in the methods is now added under the heading "Ethics and consent to participate".

8) Under the heading "Funding", please declare the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.
Response: The role of the funding body in the design, collection, and other study related activities have been now specified.

9) All results tables and figures should be placed after the References in a section called "Figures, tables additional files".
Response: A new section called "Figures, tables additional files" have been created and placed after the References.
Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
Response: Table titles have a maximum of 15 words and are included above the table. There are no legends in the tables.

Editor Comments:

This is a critical study from a very important setting. Brazil not only accounts for a significant proportion of the HIV epidemic, but it has also been a pioneer in terms of its strategic response including prevention measures. The study in question draws on existing national databases which allows for representatively and the ability to analyse a robust data set. The authors have a strong hypothesis and the dataset allows them to ask important questions about the role of treatment and "test
and treat" in preventing transmission and deaths in the community and among people living with HIV.
The analytics are very strong and the graphics and figures will be very useful for the HIV and public
health community.

REQUESTED REVISIONS:

The paper could be strengthened by a brief discussion of the scientific foundations for the hypothesis
that TasP In particular the work of Quinn (2000), Montaner (2006) Attia (2009), Granich (2009), Suthar
could add the foundation for the TasP discussion.

Response: Thanks for this comment. The second paragraph of the discussion is now dedicated to the
foundations for the hypothesis on how TasP works and relevant references have been added.

Additionally, some discussion of the 90-90-90 and 95-95-95 targets and how they relate to Brazil's
efforts would also be helpful for readers.

Response: The targets 90-90-90 and 95-95-95 targets and efforts done by Brazil has been added now in
the discussion.

Readers may also be interested in the timing of Brazil's shift to Test and treating 2013--this changed the
policy from standard WHO "test and wait" and was two years before WHO changed in 2015. The
 correlation between the change and increase in diagnoses and people being on treatment needs to be
clearly articulated to make
the case that it was the major driver.

Response: The discussion is now expanded to emphasize the early shift in the Test and Treat Initiative
in Brazil and the correlation between the change and the increase in diagnosis and treatment. The text
now included is shown below:

With the Test and Treat Initiative, Brazil adopted two years ahead from the standard WHO "test and
wait", that was only changed in 2015. The early shift in Brazil was correlated with an increase in HIV
diagnoses and patients being on treatment and might be a major driver for the observed drop in AIDS
cases. The proportion of patients with an HIV diagnosis raised from 77% in 2012 to 81% in 2015. (Brazil
Ministry of Health, 2017) As of December 2015, more than 455,000 people were receiving
antiretroviral treatment, representing an increase of 26% of PLVHA on ART (44% in 2012 and 55% in

Brazil Ministry of Health: Secretariat of Health Surveillance, Department of STI, AIDS and Viral
Hepatitis. [Report of Clinical Monitoring]. Brasília: Ministry of Health; 2017. Available at:
Other interventions that could have contributed could be mentioned but with some discussion of
potential contribution. Specifically, was PrEP being used in 2013, how much PrEP is being used now,
etc. Similarly for condoms and/or other behavioural or structural issues. To be clear from the evidence,
especially the mortality, it is clear that ART expansion has had a major preventive impact on illness,
death and transmission.

Response: the discussion now includes other interventions to better contextualize what might have
contributed to the results observed. In particular, the status of PrEP has now been described.
Reviewer reports:

Eline Korenromp (Reviewer 1):

GENERAL COMMENTS:

The study presents interesting new data, about AIDS diagnoses in Brazil including a marked drop in the last year of analysis, 2015. It is timely to evaluate the contribution of the expansion of antiretroviral treatment (the T&T initiative) to this recent drop - and the results of such analysis can usefully inform other countries starting or considering a similar expansion of treatment into T&T. However, the analysis as presented is not as strong as it could be, it misses analysis of correlates that could justify the interpretation as an effect of treatment - such as, corresponding annual new HIV diagnoses, new enrolments of PLWH on ART, the average CD4 count of PLWH enrolling in ART.

Also, I question if the observed trends are at all correctly summarized as 'decline over 2007-2015 with the most marked decline over 2014-2015'. I rather interpret the trend as something like: fairly stable levels over 2007-2014 (please assess that by statistical testing), followed by a sudden drop in 2015. Which interpretation is correct here, remains to be assessed by statistical testing of the trend, and the year(s) of interruption in the ongoing longer-term trend.

INTRODUCTION:

7th line: Mortality decrease from 5.9 to 5.6: Is this statistically significant? If not, then it seems too small a difference to interpret firmly as 'decline'…

Response: Thanks for your comment. Unfortunately, this information was obtained from the Epidemiological Bulletin of HIV/AIDS and the statistical significance was not reported. The authors agree that the statement is too strong to interpret simply as a firm decline and we have mitigated the wording.

METHODS:

Study population (page 6): Did the CD4 stay at 350/mm3 throughout 2015, or … Preferably, summarize Brazil's evolving ART eligibility criteria throughout 2002-2015 either here, or in Introduction page 4 last sentence 'PLVHA being treated with ART increased from 44% in 2012…' - rather than in bits and pieces scattered across text sections.

Response: ART eligibility criteria over time has now been included in the introduction after last sentence 'PLVHA being treated with ART increased from 44% in 2012…' as suggested.

RESULTS:

Section Changes in the AIDS detection… (page 8): 'In women, a decreasing trend was observed starting in 2011, with the largest decline between 2014 and 2015': I rather see fairly stable levels over 2008-2014, followed by an abrupt drop in 2015'. Please reconsider, and add statistical testing of the time trend (not just the overall 2007-2015, but some test of the year of curve bending, e.g. segmented regressive model of an interrupted time series.
For theory and an example of time trend testing, see:


Response: Thanks for this suggestion. A segmented regression analysis has been conducted for AIDS detection rate and for all-cause mortality rate and corresponding additions have been introduced in the abstract, methods, results, and discussion.

& Same for the corresponding sentence about the trend in males, later in the same paragraph.

Response: The corresponding sentence about the trend in females and in males have been rephrased.

Page 9, 'For heterosexuals, the proportion of reported AIDS cases was stable': For clarity, please rephrase (this sentence, and the next) as:
*The proportion of reported AIDS cases that was among heterosexuals was stable… *&… the proportion of AIDS cases who were IDUs decreased… * & … A decrease was observed in the proportion of reported AIDS cases reported as through other modes of transmission, who covered less than 1% in both sexes'.

Response: Thanks for this suggestion. The text has been modified in this new version of the manuscript.

Page 9-10: 'In other words… each year': Remove this sentence, it is redundant - and in fact possibly misleading, as this odds ratio reflects the contribution of the group to reported AIDS cases, not an absolute trend in the risk of getting infected within the underlying population (of heterosexuals, in this sentence). 'These odds ratios represented annual decreases by 10% and 11%': Same, please remove.

Response: The two sentences have been removed in the reviewed manuscript.

Add results table(s) and/or graph(s) of one or more of the following indicators (and perhaps others?), annually over 2007-2015, which would help support the interpretation of the time trends:
*HIV tests conducted
*new HIV diagnoses
*new enrolments of PLWH on ART, and/or PLWH alive on ART,
*the average CD4 count of PLWH enrolling in ART.

Response: This variables are not available in the data source analysed. We have built a table with relevant indicators obtained from several reports. The discussion has been enriched with some of this data. We propose to present this indicators as a table as supplemental material.

DISCUSSION

Page 12, In conclusion…: Again, please rephrase as something like 'fairly stable levels over 2007-2014, with a sudden drop in 2015' - depending on the result of statistical testing of the trend and year of 'interruption' of the curve.
Response: The conclusions have been rephrased as suggested and the results of statistical testing have been added. This change has also been made in the conclusions of the abstract. The first para of the discussion has been rephrased to be consistent with the conclusion.

Given that the drop in AIDS diagnosis is apparent for only one year so far, this observation and its interpretation remain to be confirmed and strengthened with similar analysis with additional years of data (2016 and 2017). Please state this as a logical next step for ongoing program evaluation.

Response: The next steps for ongoing program evaluation have been added. This change has also been made in the conclusions of the abstract.

Behavioural changes were observed … with increasing trends in homosexual….The results did not show behavioural changes. I think you meant this to refer to Figure 2c&d here? If that's the case, then please clarify and rephrase as: … 'Shifts were observed in the distribution of AIDS diagnoses by reported mode of transmission'.

Response: We totally agree with your comment and the text has been rephrased. This change has also been made in the conclusions of the abstract.

TABLE 1:

Clarify title, by inserting after 'study population': of cumulative known HIV cases (alive and/or dead?)

Response: The title of Table 1 has been clarified by inserting of cumulative known HIV cases (alive and dead) after the study population.

ACKNOWLEDGEMENTS:

Did only women participate in the study? This looks odd - was this thank-you statement inherited from a different earlier study?

Response: Thanks for noticing. The term ‘women’ has been replaced by patients.