

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence and determinants of unplanned pregnancy in HIV-positive and HIV-negative pregnant women in Cape Town, South Africa: a cross-sectional study
AUTHORS	Iyun, Victoria; Brittain, Kirsty; Phillips, Tamsin; le Roux, Stanzi; McIntyre, James; Zerbe, A; Petro, Greg; Abrams, Elaine; Myer, Landon

VERSION 1 – REVIEW

REVIEWER	Amrita Rao Johns Hopkins Bloomberg School of Public Health United States
REVIEW RETURNED	16-Nov-2017

GENERAL COMMENTS	<p>Thank you for an interesting read. I had very few comments, and feel that this paper is very well-written and offers a thoughtful take on an important topic. Some general comments below:</p> <ol style="list-style-type: none">1) I had some concerns about the potential for underrepresentation of unplanned pregnancies in your sample due to the fact that you're recruiting from presentation at an ANC visit, but I think you have addressed this adequately in the limitations.2) For the categorical variable that you created for SES, is there a reason that this was done? Why not look at each of the variables individually? Education and housing type may have different relationships with your outcome, and I wonder if some of this may be lost in the way you've categorized this.3) You used multivariable logistic regression to examine independent predictors of unplanned pregnancy, but did you consider using log binomial regression or poisson regression with robust variance estimation given the very high prevalence of your outcome?4) You say in the discussion, "Of not, levels of unplanned pregnancy were considerably higher among HIV+ compared to HIV- women, particularly those HIV-positive women not on ART. Contraceptive use mirrored these results..." I wonder why though? These results seem to be linked, and I wonder if you could add to your predictors some metric (if you have this in your database) for engagement in care (e.g. reported stigma from health care workers, ease of getting to the clinic, etc.) I think this could add a valuable angle to your piece to help explain why HIV+ women may experience a greater burden of these issues.
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REVIEWER	Monisha Sharma University of Washington, USA
REVIEW RETURNED	17-Nov-2017

GENERAL COMMENTS	<p>Overall comment: This is an interesting study but there are major methodological limitations.</p> <p>Why are odds ratios used if this is a cross sectional study? In the case of a common outcome (over 10%) the odds ratio significantly overestimates the relative risk. In this case, the outcome of pregnancy is 46%, far greater than 10%. Generally, odds ratios are used for case control studies. The authors should use a log binomial regression or poisson regression (both with robust standard errors) instead of multivariate logistic regression. More info is available here: https://stats.idre.ucla.edu/stata/faq/how-can-i-estimate-relative-risk-using-glm-for-common-outcomes-in-cohort-studies/</p> <p>Contraception availability is a likely the main driving factor for unplanned pregnancy. The higher rates seen in untested HIV-positive women and HIV-positive women not on ART area likely mostly explained by lack of access to healthcare—particularly access to contraceptives.</p> <p>Contraceptive use is not adequately discussed and likely not well controlled for in the analysis because a broad variable of any contraceptive use in the last 12 months is used. This would result in residual confounding that makes it difficult to interpret the multivariable regression.</p> <p>Generalizability of the sample to Cape Town and South Africa is unclear despite the fact that the authors list this as a strength of their analysis.</p> <p>The cross sectional nature of the study should be listed in the strengths and limitations section.</p> <p>Introduction: “Efforts to eliminate mother-to-child transmission of HIV (MTCT) continue to escalate globally, with unprecedented numbers of HIV-infected pregnant women receiving triple drug antiretroviral therapy (ART) during pregnancy and breastfeeding.”</p> <p>This sentence can be made more specific. What is the coverage of PMTCT, what is the percent reduction due to PMTCT? Replace the word unprecedented with data on the scope of the problem.</p> <p>“Despite the substantial efforts of current PMTCT programmes, MTCT remains a major driving force of the country’s HIV epidemic and in turn, an ongoing concern.” This sentence can also be much more specific.</p> <p>“Around the world, 40% of all pregnancies are estimated to be unplanned. In comparison, 55-65% of pregnancies among HIV-positive women may be unplanned.”</p> <p>What are the statistics for sub-Saharan Africa and specifically South Africa?</p>
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“Further, women who are not aware of their HIV status prior to conception may be more likely to have an unplanned pregnancy.”
How much more likely?

“In contrast, there is also some evidence to suggest that women recently initiating ART may be more likely to experience an unplanned pregnancy.”
How much less likely? A range would be useful if studies found different estimates.

It seems contraception needs and availability would be a key factor to discuss in the introduction and a very important determinant in unplanned pregnancy.

Methods:

Study design. It seems like the data for this analysis was obtained from a study with a completely different purpose so the generalizability of the sample is unclear. What were the acceptance rates for the intervention among HIV-positive and negative women. How did demographics differ between those who accepted and did not accept the intervention?

The HIV-negative women were recruited from a cohort of HIV-exposed women so they are likely higher risk than the general population. How will this sample affect your results?

“Model fit was explored using Akaike’s information criterion (AIC).”
Model confounders should have been specified A priori or included if they change the outcome by more than 10%. Choosing confounders based on model fit can result in overfitting to the data.

Results:

There is no mention of what percentage of women from the main study agreed to complete the questionnaire.

Discussion

“Nearly half (46%) of all pregnancies in this sample were reported as unplanned, evidence that levels of unplanned pregnancy remain unacceptably high in South Africa.^{15 18}

Can you be more specific about how these rates compare to others from South Africa. Replace “unacceptably high” with data.

“the current study adds to the evidence base that women who were not aware of their HIV status prior to conception and those HIV-positive not on ART may be more likely to have an unplanned pregnancy.”

What does the evidence base show? What is the increase in prevalence of unplanned pregnancy found in HIV-positive women not on ART and women not aware of their ART status? Are these estimates adjusted for important confounders?

“Our finding that unplanned pregnancy is associated with younger age, increasing parity and contraceptive use in the year prior to conception is consistent with previous research.”

What specifically does the previous research show?

“This study was specific to a single setting in South Africa and

	<p>although it is largely representative of existing sexual and reproductive practices within the country, further research is needed in other resource-limited settings.”</p> <p>No evidence is presented to back up the claim of these data being representative of South Africa. It is highly unlikely that sexual practices in Cape Town would represent rural areas of South Africa. This claim should be justified with data or removed and labeled as a limitation.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Thank you for an interesting read. I had very few comments, and feel that this paper is very well-written and offers a thoughtful take on an important topic. Some general comments below:

1) I had some concerns about the potential for underrepresentation of unplanned pregnancies in your sample due to the fact that you're recruiting from presentation at an ANC visit, but I think you have addressed this adequately in the limitations.

We agree with the reviewer and as highlighted this has been referred to in the limitations section of the study.

2) For the categorical variable that you created for SES, is there a reason that this was done? Why not look at each of the variables individually? Education and housing type may have different relationships with your outcome, and I wonder if some of this may be lost in the way you've categorized this.

Thank you for this useful comment. We adopted a psychometrically sound approach in creating the composite measure SES as utilized by Myer et al., 2008. When we included the variables home type, education and employment in the model, the adjusted ORs were similar in direction and magnitude as the estimates obtained when SES was included as a composite measure. Therefore we opted to retain SES in the model which is recommended as better able to capture variations in socioeconomic status construct especially in low and middle-income countries compared to individual proxy measures.

We have included the following sentence in the results:

'Including individual proxy measures of SES (employment, education and home type) in the adjusted model did not change our main findings. The adjusted odds ratio of an unplanned pregnancy with individual proxy measures of SES (compared to HIV negative women) was AOR 1.43; 95% CI: 1.05-1.94 in newly diagnosed HIV-positive women, 1.56; 95% CI: 1.13-2.15 for previously diagnosed HIV positive women not on ART and 1.10 95% CI 0.82-1.47 for previously diagnosed HIV positive women on ART. In comparison, SES was included as a composite measure, the adjusted odds ratio of an unplanned pregnancy (compared to HIV negative women) AOR 1.43; 95% CI: 1.05-1.94 in newly diagnosed HIV-positive women, 1.56; 95% CI: 1.13-2.15 for previously diagnosed women not on ART and 1.10; 95% CI: 0.82-1.47 for previously diagnosed HIV positive women on ART'

3) You used multivariable logistic regression to examine independent predictors of unplanned pregnancy, but did you consider using log-binomial regression or Poisson regression with robust variance estimation given the very high prevalence of your outcome?

Thank you for this comment. We acknowledge the limitations of using a logistic regression given the high prevalence of our outcomes. We have therefore explored identifying predictors of unplanned pregnancy using a log-binomial regression model. Our main findings remain the same and we have revised the result section accordingly. (See Table 4. in revised manuscript)

4) You say in the discussion, "Of note, levels of unplanned pregnancy were considerably higher among HIV+ compared to HIV- women, particularly those HIV-positive women not on ART. Contraceptive use mirrored these results..." I wonder why though? These results seem to be linked, and I wonder if you could add to your predictors some metric (if you have this in your database) for engagement in care (e.g. reported stigma from healthcare workers, ease of getting to the clinic, etc.) I think this could add a valuable angle to your piece to help explain why HIV+ women may experience a greater burden of these issues.

Thank you for this useful comment. We agree with the reviewer that the higher levels of unplanned pregnancy among HIV positive women compared to HIV negative women suggest a difference in access to health care services, impact of stigma and health-seeking behaviours between the two groups. Also, HIV positive women not on ART may not have accessed any other health care services and consequently had limited access to contraceptives and other reproductive health services. Unfortunately, these additional risk factors were not measurable from the data available.

Reviewer 2:

Overall comment:

This is an interesting study but there are major methodological limitations.

1) Why are odds ratios used if this is a cross-sectional study? In the case of a common outcome (over 10%) the odds ratio significantly overestimates the relative risk. In this case, the outcome of pregnancy is 46%, far greater than 10%. Generally, odds ratios are used for case-control studies. The authors should use a log-binomial regression or Poisson regression (both with robust standard errors) instead of multivariate logistic regression. More info is available here:

<https://stats.idre.ucla.edu/stata/faq/how-can-i-estimate-relative-risk-using-glm-for-common-outcomes-in-cohort-studies/>

Thank you for this comment. We take into consideration that a log-binomial or Poisson regression is appropriate given the high prevalence of the outcome in our study. We have examined predictors of unplanned pregnancy using a log-binomial regression method and have revised the result section accordingly, as per the table below. Nevertheless, the effect size and direction of our findings remain similar (See Table 4. in revised manuscript).

2) Contraception availability is a likely the main driving factor for unplanned pregnancy. The higher rates seen in untested HIV-positive women and HIV-positive women not on ART area likely mostly explained by lack of access to healthcare—particularly access to contraceptives.

Thank you for this useful comment. In as much as lack of access to healthcare (family planning) commonly explains high levels of unplanned pregnancy, we feel that this was not a major contributing factor to unplanned pregnancy in our population. Free family planning services is offered and widely available in our study setting.

We have revised the discussion section to further expand on how contraceptives may have influenced unplanned pregnancy in our population.

3) Contraceptive use is not adequately discussed and likely not well controlled for in the analysis because a broad variable of any contraceptive use in the last 12 months is used. This would result in residual confounding that makes it difficult to interpret the multivariable regression.

Thank you for this point. We agree with the point raised, however we were restricted in terms of variables structure on contraceptives available in the database. We take into consideration that residual confounding may be present with respect to contraceptive use and its influence on unplanned pregnancy and have already addressed this as a limitation in the discussion section:

'Finally, as contraceptive use was assessed only as any use of a contraceptive method in the 12 months prior to pregnancy recognition, our data are not robust to assess consistent contraceptive use during this time.'

4) Generalizability of the sample to Cape Town and South Africa is unclear despite the fact that the authors list this as a strength of their analysis.

Thank you for this comment. We acknowledge that our sample may not be generalizable to other parts of South Africa. We have addressed this issue as per other comments in the discussion section. We have also addressed this as a limitation generalizability of our findings in the 'Strengths and Limitations' section of the manuscript:

'Although the findings of this study is largely representative of existing sexual and reproductive practices within the country, it may not be generalizable to other resource-limited settings.'

5) The cross-sectional nature of the study should be listed in the strengths and limitations section. We agree with the reviewer. The strengths and limitations section of the manuscript has been revised to reflect this limitation.

Introduction:

1) "Efforts to eliminate mother-to-child transmission of HIV (MTCT) continue to escalate globally, with unprecedented numbers of HIV-infected pregnant women receiving triple-drug antiretroviral therapy (ART) during pregnancy and breastfeeding." This sentence can be made more specific. What is the coverage of PMTCT, what is the percent reduction due to PMTCT? Replace the word unprecedented with data on the scope of the problem.

We have revised this sentence to include specific estimates on PMTCT coverage:

'Efforts to eliminate mother-to-child transmission of HIV (MTCT) continue to escalate globally and advances in prevention of mother-to-child transmission (PMTCT) services have led to significant reductions in the number of new paediatric infections across resource-limited settings including Africa.¹ In South Africa, over 95% of HIV-infected pregnant women receiving triple-drug antiretroviral therapy (ART) during pregnancy and breastfeeding and the rate of MTCT decreasing from 8% in 2008 to 1.3 % in 2016.

2) "Despite the substantial efforts of current PMTCT programmes, MTCT remains a major driving force of the country's HIV epidemic and in turn, an ongoing concern." This sentence can also be much more specific.

We agree with the reviewer and revised this sentence accordingly:

'Despite the substantial efforts of current national PMTCT programmes, MTCT remains a major contributor to new paediatric infections accounting for an estimated 12,000 new infections in 2016, and in turn, remains a major concern (UNAIDS 2017 estimates).'

3) "Around the world, 40% of all pregnancies are estimated to be unplanned. In comparison, 55-65% of pregnancies among HIV-positive women may be unplanned." What are the statistics for sub-Saharan Africa and specifically South Africa?

Thank you for this valid point. We have revised this sentence to include prevalence estimates of unplanned pregnancy in sub-Saharan Africa and Africa.

'An estimated 40% of all pregnancies worldwide and 35% pregnancies in Africa are unplanned. In comparison, 35-65% of pregnancies among HIV-positive women across sub-Saharan Africa may be unplanned with 60-62% of unplanned pregnancy recorded among HIV-positive women in South Africa.'

4) "Further, women who are not aware of their HIV status prior to conception may be more likely to have an unplanned pregnancy." How much more likely?

We acknowledge the reviewer's concern and have revised the sentence accordingly.

'Further, women who are not aware of their HIV status prior to conception may be more likely to have an unplanned pregnancy. Findings from a recent study in Botswana demonstrated an almost 2-fold increase in the likelihood of unplanned pregnancy among women unaware of their HIV-positive serostatus prior to conception compared to those who were aware'

5) "In contrast, there is also some evidence to suggest that women recently initiating ART may be more likely to experience an unplanned pregnancy." How much less likely? A range would be useful if studies found different estimates.

Thank you. We have revised the sentence.

'In contrast, there is also some evidence to suggest that new pregnancy rates are significantly higher for women on ART compared to those not on and approximately 60% of HIV-positive women on ART experience an unplanned pregnancy.'

6) It seems contraception needs and availability would be a key factor to discuss in the introduction and a very important determinant in unplanned pregnancy.

We agree with the reviewer. We have included additional information on contraceptive needs and coverage in the introduction section.

Methods:

1) Study design. It seems like the data for this analysis was obtained from a study with a completely different purpose so the generalizability of the sample is unclear. What were the acceptance rates for the intervention among HIV-positive and negative women. How did demographics differ between those who accepted and did not accept the intervention?

Thank you for this comment. The parent studies consecutively enrolled HIV-infected pregnant women and a comparator cohort of uninfected women at their first antenatal visit at a primary-level antenatal care facility in a semi-urban area in Cape Town, South Africa. There is a high antenatal clinic coverage in our study setting (>95%), therefore data for our study sample drawn from existing datasets is largely representative of our study setting.

2) The HIV-negative women were recruited from a cohort of HIV-exposed women so they are likely higher risk than the general population. How will this sample affect your results?

Thank you for this comment. HIV-negative women were randomly sampled from women presenting for antenatal care at a routine ANC clinic within the same community as the HIV-positive women. Considering the high rate of antenatal clinic coverage, our study participants were representative of the population within the community where we recruited. We were unable to assess the potential impact of risk set differences between HIV-negative women in our sample and those in the general population as this was outside the scope of this study.

3) "Model fit was explored using Akaike's information criterion (AIC)." Model confounders should have been specified A priori or included if they change the outcome by more than 10%. Choosing confounders based on model fit can result in overfitting to the data.

Thank you for this useful comment. Confounders were selected a priori for the model and we used AIC with a priori hypothesis about confounders namely age, and SES to assess model fit. We have however revised the relevant sentences under 'statistical analysis' in the Methods section to clearly highlight our procedures:

'A multivariable logistic regression model was built to examine independent predictors of unplanned pregnancy, with maternal age and SES considered as a priori confounders. Model fit was explored using Akaike's information criterion (AIC) and a priori hypothesis about confounders namely maternal age and SES'

Results:

1) There is no mention of what percentage of women from the main study agreed to complete the questionnaire.

Thank you for this comment. We did not include the proportion of women who completed the questionnaire as all women recruited into both parent studies agreed to complete the London Measure of Unplanned Pregnancy and data for this cross-sectional analysis included only participants who had complete responses for the London Measure of Unplanned. This information although useful for understanding potential bias in the parent studies was of less significance in our study.

Discussion:

1) "Nearly half (46%) of all pregnancies in this sample were reported as unplanned, evidence that levels of unplanned pregnancy remain unacceptably high in South Africa.^{15 18}

Can you be more specific about how these rates compare to others from South Africa. Replace "unacceptably high" with data.

We thank the reviewer for this comment. We have revised the sentence as follows:

'Nearly half (46%) of all pregnancies in this sample were reported as unplanned. Similar to high levels of approximately 60% of unplanned pregnancy previously reported in South Africa.'

2) "the current study adds to the evidence base that women who were not aware of their HIV status prior to conception and those HIV-positive not on ART may be more likely to have an unplanned pregnancy."

What does the evidence base show? What is the increase in prevalence of unplanned pregnancy found in HIV-positive women not on ART and women not aware of their ART status? Are these estimates adjusted for important confounders?

Thank you for this comment we agree that this explanation is unclear at this time, and we have edited the text to state that our conclusion is only suggested by our results:

'Although previous research has demonstrated slightly higher levels of unplanned pregnancy reaching up to 62% among HIV-positive women on ART,^{15 26} the current study provides additional evidence that women who were not aware of their HIV status prior to conception and those HIV-positive not on ART may be more likely to have an unplanned pregnancy.¹⁹

3) "Our finding that unplanned pregnancy is associated with younger age, increasing parity and contraceptive use in the year prior to conception is consistent with previous research." What specifically does the previous research show?

Thank you for this comment. We have revised the discussion section.

4) "This study was specific to a single setting in South Africa and although it is largely representative of existing sexual and reproductive practices within the country, further research is needed in other resource-limited settings. "No evidence is presented to back up the claim of these data being representative of South Africa. It is highly unlikely that sexual practices in Cape Town would represent rural areas of South Africa. This claim should be justified with data or removed and labelled as a limitation.

Thank you for this comment. We acknowledge that this statement was more ambiguous than intended, we have therefore adjusted the text to be clearer and include additional evidence to support our claim:

'This study was specific to a single urban setting in South Africa and although it is largely representative of existing knowledge of contraceptive methods, uptake and method preference within similar settings across the country, further research is needed in other resource-limited settings.'

VERSION 2 – REVIEW

REVIEWER	Amrita Rao Johns Hopkins School of Public Health USA
REVIEW RETURNED	07-Jan-2018
GENERAL COMMENTS	No additional comments

VERSION 2 – AUTHOR RESPONSE

Response to editor's comments: (Editor's comments in bold)

Editor Comments to Author:

We noted that in your methods section (page 7) your revised manuscript refers to the use of multivariate logistic regression. You state that "A multivariable logistic regression model was built" however you indicated that you have replaced the multivariable logistic regression model previously reported in your manuscript with the use of a log-binomial regression model. Please can you clarify this and modify your methods section accordingly.

Thank you for this comment. We acknowledge the discrepancy highlighted. A log-binomial regression was built, therefore we have modified the methods section accordingly.

Response to reviewer's comments (Reviewer's comments in bold)

Reviewer 1:

Please state any competing interests or state 'None declared': None declared

Thank you for this comment. The relevant text has been revised.