

Author's response to reviews

Title: The impact of Provider-Initiated (Opt-out) HIV Testing and Counselling of patients with sexually transmitted infection in Cape Town, South Africa. A controlled trial

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Author's response to reviews: see over

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Dear Sir

Addressing the reviewers' comments: MS: 1913522488306811

Thank you for considering this manuscript for publication and for the useful comments provided by the reviewers. The reviewers' comments are addressed below and additional information on base-line adjusted analysis is provided in the appendix to this letter.

In addition to the changes to the text that are detailed below, other edits were made in the manuscript to improve the flow of the document. These are:

1. The last sentence of the Abstract was changed and now reads (pg.4):

Recommendations are made for increasing the impact and feasibility of PITC in high HIV prevalence and resource-constrained settings, including flexible use of clinical and lay staff and combining PITC with VCT and other community-based approaches to HIV testing.

2. The Results section has been changed; we added details on the baseline adjustment.
3. The Discussion section has been changed slightly in paragraph one, two and six and we moved one paragraph to the Conclusion section.

Reviewer 1. Theresa Munyombwe

Are methods appropriate and well described, and are sufficient details provided to replicate the work.

2.1 The authors demonstrated how sample size was determined taking into account clustering sampling. An ICC of 0.08 was used but it was not justified. Is it from previous studies? If yes give references.

To address this query, the explanation of sample size has been changed in the text from sample size **calculation** to sample size **validation** as this describes more accurately what was done. The justification for the ICC and a reference are also supplied. The paragraph now reads as follows (pg. 9-10):

A sample size validation was done given that the intervention arm would consist of 7 intervention clinics. With this restriction, the study would be able to show an increase of 20%

in testing rate from an estimated baseline of 30%, with 80% power, at a 5 % significance level and using an intra-class correlation coefficient (ICC) of 0.08 and a cluster size of 90. In a recent review of ICCs in 188 health systems research studies, the median ICC used was .051 (IQR 0.011 to .094). The ICC of 0.08 in this study is closer to the conservative end of this range.[31] We doubled the control group to 14 clinics to increase the power of the study. Based on available data, we assumed a cluster size of 90 new STI patients per quarter per clinic.

2.2 The design is flawed in terms of randomisation. There is no random allocation of treatments to clinics.

The lack of randomization is stated in the methods (pg 8) and acknowledged as a limitation in the text: (pg 21):

Pg 8: “pragmatic cluster non-randomised controlled trial”

Pg 21: “The lack of randomization of clinics to intervention and control groups introduces the risk of bias for the study outcomes.”

2.3 One would wonder whether the studied clinics are representative of all the clinics or there is selection bias.

This is a limitation of the study that is acknowledged. The top management and local managers wanted to select clinics that were serving a wider community across the whole of the city and so the sites were spread out across districts and unfortunately not randomised. The method of selecting clinics has been made somewhat more explicit in the text on pg. 9 and now reads:

A project steering committee in consultation with local district managers selected a representative clinic from each district.

2.4. Assessors were also not blinded this could result in assessment bias.

This limitation is acknowledged and stated in the paper on pg. 21 and reads:

In the absence of blinding, factors such as staff enthusiasm and increased monitoring could have had a modifying effect.

There were two assessors who were not blinded, but they followed a standard protocol for both the intervention and the control clinics in terms of accessing the centralized routine data on new STI patients and the clinic-based counselling registers. Records were checked for completeness and the data extraction from the registers was done by an independent data manager.

3. Statistical methods

3.1 The statistical methods are sound and some of the assumptions of the tests were checked except the normality assumption for the t test. Can the authors check the normality assumption for the response variable?

The normality assumption was checked. Distribution of all the three the main outcomes have an approximate, though not exact, symmetrical distribution for

which the t-test is adequate and robust for comparing two samples. Small sample sizes have low power when testing this assumption. We added the following sentence on pg. 13:

We checked the normality assumption of the t-test.

3.2 The authors have used a one sided test for all the comparisons except the comparison of 26.7% and 13.5%. What is the reason for changing?

A one-sided t-test was not used for the comparison because we did not hypothesize about any direction in the proportion of patient who declined testing. This clarification was added to the bottom of table 3, pg. 32 with the following sentence:

**Two-sided t-test since no direction was hypothesized.

3.3 On page 15 of the paper, the total for control offered HIV testing is given as 3407 yet table 2 shows 3406. The average is given as 50.9% for the control group yet table 2 shows 50.7%.

This error has been corrected on pg. 15 which now reads:

Patients were also more likely to be offered HIV testing in the intervention clinics: intervention clinics offered the HIV test to 2326 (76.8%) of new STI patients compared with 3406 (50.7%) in the control group (p=0.0029).

3.4 The results of the multinomial logistic regression were not reported. Why did the authors exclude these results?

The results are now included on pg. 16 which reads:

From the multinomial regression (adjusted for clustering) on the composite testing outcome (tested, offered, not tested) the odds ratio for being tested is 2.24 (95% CI: 1.12 to 4.46), p=.022 for the intervention group compared to the control group. The odds ratio is 3.35 (95% CI: 1.42 to 8.79), p=.007 for 'not tested' in the intervention group compared to the control group. These results confirm the outcome specific comparison reported above and in Figure 2 and Table 3.

4. Are the data sound and well controlled?

4.1 Are age and sex the only patient demographic characteristics that needed to be balanced at baseline?

We do not have a baseline comparison of age and gender of STI patients or of HIV testing rates for STI patients, so in Table 1 we were limited to data on clinic-based characteristics that we thought might be associated with the outcome. Age and sex sub-analysis were only done on the outcome data: for those offered testing and tested as this information was available in the counselling registers used for the outcome data.

5. Statistical review: Yes, and I have assessed the statistics in my report.

The statistical review was conducted, evidence of which are provided in addressing the comments above. The rationale for not including the baseline- adjusted analysis is further clarified in the manuscript. For transparency, the detailed analysis is attached as an appendix to this letter.

Reviewer 2: Seth Kalichman

1. The study design is sound. However, there are concerns with the data analyses. The Study design randomized clinics to conditions but it seems individuals were treated as the unit of analysis.

The study did not randomise clinics and this is stated on pg. 8:

The design was a pragmatic cluster non-randomised controlled trial, in which 7 clinics were selected to receive the intervention and 14 clinics served as control clinics.

The analysis was done at clinic level and this is stated on pg. 13. To clarify further, the sentence was changed and a reference was added. It now reads:

These proportions were utilized as clinic level outcomes and used to compare the two groups. This clinic level analysis accounts for the clustering within clinics.[34]

2. The nesting that occurred in the design does not appear to be accounted for in the statistical approach. If the analysis was indeed nested, then the data analysis section should be more clearly described.

As stated above, the analysis was done at clinic level and this is stated on pg. 13: We added the result of the multinomial analysis that also states that the analysis was clustered/nested (See point 3.5 for reviewer 1 above).

3. Another concern with the data analyses is that the baseline values were not adjusted. The author states that a test of quality showed homogeneity of variance. However, adjusting for baselines provides a true test of the intervention effect over and above baseline. It is not so much whether groups differ at baseline. Rather, the idea is to control for baseline. Baseline values are correlated with follow-up. It is this variance that should be controlled in the analysis.

The baseline adjusted analysis was done as recommended by the reviewers and the details are attached in the appendix to this letter. The relevant changes were made in the manuscript as detailed below. In the Method section, pg. 14, the sentence was changed and now reads:

The statistical adjustment for baseline differences is not reported and this is considered in the results and in the study limitations.

The following explanation was added to the Results section on pg. 15:

As mentioned earlier, the adjusted baseline analysis is not used. The inverse association observed between the baseline variable of a broader population and the much narrower study population may lead to a distorted estimate of the intervention effect. The unadjusted results reported in the manuscript is a more conservative estimate of the intervention effect when compared to the adjusted estimate given in this analysis (13.7% compared to 22.2%). We feel that the unadjusted result is a more reasonable result with respect to the health system setting in which this was done.

The following discussion was added to the study limitations on pg. 21:

The one baseline testing variable (HIV test acceptance, VCT) that was significantly different across intervention and control sites was inappropriate as a measure of baseline differences, for the following reasons. This variable is not strictly comparable to the main outcome in this study as it refers to the proportion of general clinic patients who were tested as a proportion of those who received pre-test counselling by lay counsellors in the VCT service. It covers a different and much larger general patient target group (and not STI patients only) and refers to a different testing service (VCT), delivered by lay counsellors and not clinicians. However, given the lack of baseline data on the main outcome, we felt that this 'HIV test acceptance rate' variable should be examined in the baseline comparison of the two groups and that unadjusted outcome measures should be presented.

4. The significant difference in declining testing was not favourable to the intervention condition. This is an important result. I think a bit more discussion of its implications is warranted.

This result is acknowledged and stated in the text on pg 18. Additional discussion has been added to take the reviewer's comment into account. It now reads:

More than one quarter of patients offered testing in the intervention group declined to test (double that in control group), a result that is not favourable to the intervention. The result is understandable given that patients did not self-initiate testing as in the case of the VCT. Nevertheless, it represents another area where the impact of the PITC intervention could be improved substantially if the proportion who decline testing is reduced. This can be done by staff using more effective motivation strategies to encourage patients to test, provided that it does not compromise patient informed consent. In terms of the ethical implementation of the PITC approach, the high test refusal rate could be considered indirect evidence that patients were able to exercise their right to decline testing.

5. Overall this is a well conducted study. The data analyses require further attention as do the discussion of implications of the findings.

The authors reviewed the data analyses as discussed in our responses above. We provide more detail in the appendix on the baseline-adjusted analysis.

Reviewer 3: Mike English

Clarifications:

- 1. It is not quite clear whether this was planned a priori as an intervention trial or whether it was an opportunistic evaluation of a programme intervention – at the start of the methods it is implied that the intervention was planned and initial PHC clinics identified before the investigators were involved – could this be clarified?**

The health manager asked for a systematic external evaluation of the impact of the intervention. In the absence of randomization, control clinics were added and a baseline comparison done. The following sentence was added in the Method section, pg 8:

This was an opportunistic evaluation of an intervention programme undertaken by the health authority.

- 2. Was it possible for the control groups to decline participation? If not the fact that two clinics in the intervention group opted out and provided no data might represent a considerable bias – especially as the reason given was operational difficulties in which case the intervention may only be effective in 2/9 = 78% of clinics which means the overall effectiveness is what is reported x 0.78.**

One control clinic declined participation. This clarification was added to the text on pg. 9:

Nine intervention sites were initially selected but two clinics declined participation shortly before implementation, citing operational difficulties. *One control clinic opted out citing similar reasons.* The remaining fourteen eligible clinics became the comparison group. There was no matching of clinics but statistical comparison of clinics at baseline was conducted retrospectively.

We started with 24 clinics we considered as eligible in that they met the criteria and would have the systems to implement the intervention. When it came to implementation, two intervention clinics decided to opt out and one control clinic, for the same reasons of capacity and operational difficulties. We decided not to use an Intention to Treat (ITT) analysis in this study as we wanted to know the effectiveness of the PITC intervention in clinics that actually implemented the intervention. We added a sentence to this effect on pg 13 in statistical methods.

Only the clinics that were operationally able to implement the protocol and provide outcome data to the trial were included in the analysis since we wanted to know the effectiveness of the PITC intervention in clinics that actually implemented the intervention.

- 4. Was there any justification for an ICC of 0.08 in the sample size estimation?**

This issue is addressed in our response to reviewer 1, point no. 2.1 above.

4. Was the baseline, pre-intervention data collected prospectively or retrospectively?

The pre-intervention baseline data was collected retrospectively using routine administrative data. The sentence in the text was revised to read as follows on pg.9:

There was no matching of clinics but statistical comparison of clinics at baseline was conducted using routine administrative data that was collected retrospectively.

5. For data checking it is not quite clear if the corrections to age, sex were made only to the 10% sample or whether the whole dataset was re-checked and re-entered? For further discussion (perhaps after further statistical input as I have no great expertise).

Data checking was done for completeness of all clinic records before and during data entry. The 10% sample check at the end identified a particular clinic where there were anomalies in the data and this was corrected. The whole data set was not rechecked and re-entered. This section in the text was changed to clarify and now reads (pg.13):

The 10% sample check at the end identified a particular clinic where there were anomalies in the data (mainly for sex and age) and this was corrected. This did not require a rechecking and re-entry of the whole data set.

6. In the analyses it is stated that no adjustment for baseline characteristics was required. This is a puzzling statement given that the clinic selection was not random and that the sample, being based on clusters, is of necessity quite small. It may not be easy (or that effective) to try adjusting for baseline imbalance but I would not agree that it is as easy as saying it is 'not required'. As an example although providing useful qualitative data to explain that the baseline imbalance in HIV test acceptance was unlikely to explain the difference in study groups at the endpoint could this baseline imbalance not be adjusted for in the multinomial regression?

The baseline adjusted analysis was done as recommended by the reviewers and the details are attached in the appendix to this letter. For a detailed response to the above query, please see reviewer 2, point no.3, above.

APPENDIX

Adjustment for Baseline

- Analysis was done at clinic level for outcome as well baseline measurement.
- Simple linear regression was performed
- **Outcome: percentage of STI patients tested for HIV**
- **Baseline variable: percentage of VCT testing in the general clinic population**

Analysis

Model testing for interaction between group and baseline vct testing in the general clinic population (variable 8 Table 1)

```
. xi: regress pertested i.group vctaccept i.group*vctaccept
i.group          _Igroup_0-1          (naturally coded; _Igroup_0 omitted)
i.group*vctac~t  _IgroXvctac_#       (coded as above)
```

Source	SS	df	MS	Number of obs =	21
Model	2636.10041	3	878.700135	F(3, 17) =	2.45
Residual	6094.21066	17	358.48298	Prob > F =	0.0987
				R-squared =	0.3019
				Adj R-squared =	0.1788
Total	8730.31106	20	436.515553	Root MSE =	18.934

pertested	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
_Igroup_1	-53.06114	143.4328	-0.37	0.716	-355.6778 249.5555
vctaccept	-111.0628	50.33592	-2.21	0.041	-217.2624 -4.863348
_IgroXvcta~1	81.6868	155.3353	0.53	0.606	-246.0421 409.4157
_cons	136.7445	42.94091	3.18	0.005	46.14709 227.3419

Comment

- **Interaction not significant**

Model with adjustment for baseline VCT testing (variable 8 Table 1) only

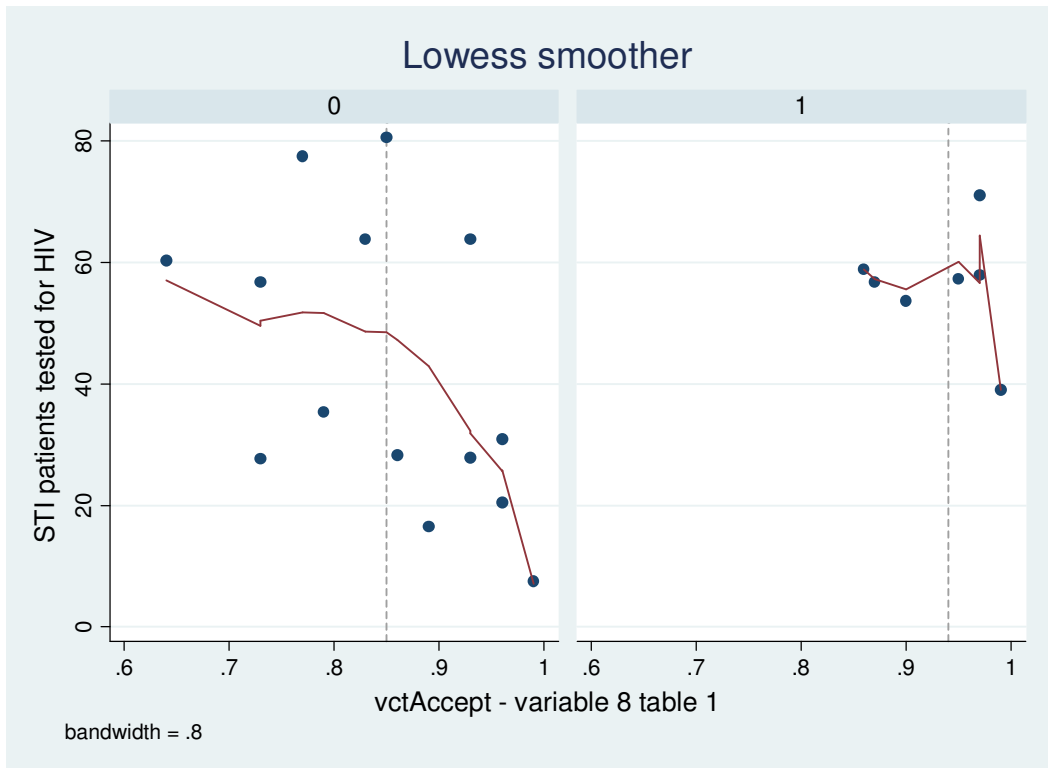
```
. xi: regress pertested i.group vctaccept
i.group          _Igroup_0-1          (naturally coded; _Igroup_0 omitted)
```

Source	SS	df	MS	Number of obs =	21
Model	2536.9643	2	1268.48215	F(2, 18) =	3.69
Residual	6193.34677	18	344.07482	Prob > F =	0.0455
				R-squared =	0.2906
				Adj R-squared =	0.2118
Total	8730.31106	20	436.515553	Root MSE =	18.549

pertested	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
_Igroup_1	22.19686	9.416619	2.36	0.030	2.413279 41.98044
vctaccept	-102.4852	46.65306	-2.20	0.041	-200.4997 -4.470775
_cons	129.478	39.83152	3.25	0.004	45.79509 213.1609

Comment

- **Estimated intervention effect is 22.2% (95% CI: 2.4 to 42.0), p=.03.**
- **This enhancement of the intervention effect is due to the inverse association between baseline VCT testing in the general clinic population (variable 8 Table 1) and HIV testing of STI patients.**
- **See graph of the two groups below.**



Baseline mean VCT acceptance value indicated for both groups. (0=control, 1=intervention)
Lowess smoother used to estimate regression line.

Discussion

- **A baseline adjustment was done for the variable 8 Table 1: HIV test acceptance (VCT)**
- **This variable refers to the percentage of general patients who were counseled and tested in the VCT service at baseline.**
- **The STI patient population is a small but unknown subset of this population as they were not uniquely identified at baseline.**
- **The percentage STI patients tested for HIV in the study period is different from the general VCT population described at baseline above (Variable 8 Table 1).**
- **The unadjusted results reported in the manuscript is a more conservative estimate of the intervention effect when compared to the adjusted estimate given in this analysis. (13.7% compared to 22.2%). We feel that the unadjusted result is a more reasonable result with respect to the health system setting in which this was done. The inverse association observed between the baseline variable of a broader population and the much narrower study population may lead to a distorted estimate of the intervention effect.**
- **The following paragraph was added to the discussion of limitations of the study:**

The one baseline testing variable (HIV test acceptance, VCT) that was significantly different across intervention and control sites was inappropriate as a measure of baseline differences, for the following reasons. This variable is not strictly comparable to the main outcome in this study as it refers to the proportion of general clinic patients who were tested as a proportion of those who received pre-test counselling by lay counsellors in the VCT service. It covers a different and much larger general patient target group (and not STI patients only) and refers

to a different testing service (VCT), delivered by lay counsellors and not clinicians. However, given the lack of baseline data on the main outcome, we felt that this 'HIV test acceptance rate' variable should be examined in the baseline comparison of the two groups and that unadjusted outcome measures should be presented.