Author's response to reviews

**Title:** A comparison of linkage to HIV care after provider-initiated HIV testing and counselling (PITC) versus voluntary HIV counselling and testing (VCT) for patients with sexually transmitted infections in Cape Town, South Africa.

**Authors:**

Natalie Leon (natalie.leon@mrc.ac.za)
Catherine Mathews (catherine.mathews@uct.ac.za)
Simon Lewin (simon.lewin@mrc.ac.za)
Meg Osler (meg.osler@uct.ac.za)
Andrew Boulle (andrew.boulle@uct.ac.za)
Carl Lombard (carl.lombard@mrc.ac.za)

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**Author's response to reviews:** see over
2 July 2014

Dear BMC Editorial Team

Thank you for providing us with this peer reviewed report which we found to be very thorough and useful for improving the article.

We have responded to the reviewer’s comments point by point in the 10-page table below. We revised the article in response to the comments and provide extracts from the manuscript to illustrate where changes have been made.

We hope that you will find our responses and revisions satisfactory.

Please let us know if there are any additional matters you would like us to attend to that could assist your deliberations on the publication of this article.

Thanking you.

Sincerely

Dr. Natalie Leon

Responses to the Reviewer’s report

**Title:** A comparison of linkage to HIV care after provider-initiated HIV testing and counselling (PITC) versus voluntary HIV counselling and testing (VCT) for patients with sexually transmitted infections in Cape Town, South Africa.

**Reviewer:** Bruce Larson

Thank you for the thorough and helpful review of this paper. Our responses to the reviewer’s comments are provided below.

**Reviewer’s report:**
Reviewer Comments
General: This is a nicely presented paper on an important topic. I have some general comments and suggestions for the authors to consider. I only have three somewhat major comments:
<table>
<thead>
<tr>
<th>Reviewer Comments</th>
<th>Authors’ response</th>
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<tbody>
<tr>
<td>1. I would have preferred the analysis to have the same possible follow up time for each patient (e.g. 1 year after HIV testing for a CD4 test result; and 1 year after a CD4 result for a viral load test, or two years for each, etc.).</td>
<td>We agree that having a standard follow-up time for each patient and for each of the outcomes of interest (CD4 test done and viral load test done) would have been preferable and that this is a limitation of the study. This limitation was mainly due to the logistics and pragmatic context of the study and in retrospect, we should have made the decision in favor of standardizing the follow-up period across patients, even if this meant shortening the follow-up period. To explain our decision-making; the retrospective review of the cohort was done up to the point when data was available from the National Health Laboratory Service (NHLS), in December 2007. This meant that we would only have been able to standardize the follow-up period for 6 months (as the last date for HIV testing in the cohort was June 2007). For viral load tests, the search of the electronic NHLS data base was done when data on viral load tests was available up to December 2008. This means that we could have standardized the follow-up period for viral load test records for a 12 month period, ending June 2008 (as the last HIV testing was done in June 2007). We opted for extending the duration of the observation period and to make use of the available data up to December 2008. For pragmatic reasons, it was thought that information on follow-up over a longer period may be of value to the health managers who were interested in the outcome of the evaluation, but this was done at the expense of standardising the follow-up period. We acknowledge that in retrospect, this approach limited the robustness of the method. We expanded on this limitation in the Strengths and limitations section of the paper, on page 2, which now reads: (see shaded section) Although the study allowed for a reasonably long timeframe for follow-up periods, this may still be a limited time interval (as viral load testing may only have been done 9 months after a patient was initiated on ART). Nevertheless, the study design would have been strengthened if the follow-up period was standardised for all patients, even if this meant a shortened observation period. We also made this more explicit by adding this as a recommendation for future research on pg 21, which now reads: Further studies should consider both standardising and extending the follow-up period and should include investigation of follow up care for pre-ART patients (for example, monitoring 6 monthly follow-up CD4 testing for pre-ART patients).</td>
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<tr>
<td>2. In South Africa, a CD4 test result show up in the NHLS database whether the</td>
<td>We agree with your assessment that having a laboratory record of a CD4 test is limited as an indicator of a patient being linked to care. It gives no indication of whether the patient actually received that</td>
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</table>
patient actually received
the result or not. Thus, your
definition of 'linkage to
care' remains a bit vague.
At least in some locations
where I’ve worked, once a
person tests positive for
HIV, the majority then
provide a blood sample of
CD4 testing at the same
visit. So, in this case a CD4
result will exist, whether or
not the patient ever returns
to collect the result.

laboratory test result, which is off course, a pre-requisite for the
patient seeking access to follow-up care (especially at the early stage of
seeing to link patients to follow-up care via their CD4 test result).
Therefore, as you point out, using the existence of a CD4 test result as
proxy for follow-up care, could be overstating the level to which
patients may have been offered follow-up services. At the time of this
study, the practice of drawing blood for a CD4 test on the same day
was varied, thought it would appear this was the predominant
practice in this study patient population also.

We added information in the Methods section to acknowledge this
point more explicitly (pg. 7-8). It now reads:

Access to these tests was used as a proxy for whether patients
received the appropriate type of care, though it is acknowledged that
this is not a comprehensive indicator of linkage to care. The existence
of a laboratory test record does not indicate that the patient returned
and was informed of the test result and this is noted when discussion
the strengths and limitations of the study.

And in the Discussion section we added a sentence to draw attention
to the limitation (pg. 15-16), which now reads:

Most CD4 tests in both arms were done within less than a week of
HIV testing and this, together with the relatively high level of CD4
tests done, point to a strength of the health service in terms of
ensuring that appropriate blood tests are done as the first stage in
linkage to care. However, this indicator cannot tell us what
proportion of those with CD4 test record actually returned to the
clinic and was informed of the test result.

And this point was noted in the Strengths and limitation section on
pg.21:

Finally, the study was not able to ascertain what proportion
of patients with a CD4 record actually returned to the clinic to get their
CD4 test result, nor was it able to examine the reasons for the gaps in
linkage to care, or to assess quality of care received.

And in the Discussion section, this issue is included as a
recommendation for further research, pg. 21:

Further studies should consider both standardising and extending the
follow-up period and should include investigation of follow up care
for pre-ART patients (for example, monitoring 6 monthly follow-up
CD4 testing for pre-ART patients). The introduction of the patients’
identity number (as a unique patient identifier) in routine records
and/or for research purposes, could help to track mortality, as was
done in a more recent trial on nurse-initiated ART [38].
3. The majority of patients with a CD4 result are not ART eligible. It is not clear why they were excluded from the analysis. You could have looked at if they had another CD4 test result with a certain follow up period (say 8 months if guidelines were every 6 months).

We agree that the study would have benefitted from broadening the scope of the follow-up interventions, to identify CD4 test records for those who were not yet eligible for ART. In retrospect, this is an oversight, influenced to a large extent, by the logistics of the search process. The searching for CD4 records relied heavily on manual cross-referencing of a large database of laboratory records and was done before we had access to the software that allowed us to more easily do the cross-referencing for viral load records for ART-eligible patients. We included this a recommendation in our manuscript and have now made this more explicit by adding further explanation. It now reads (pg.21):

Further studies should consider both standardising and extending the follow-up period and should include investigation of follow up care for pre-ART patients (for example, monitoring 6 monthly follow-up CD4 testing for pre-ART patients).

Other comments, suggestions, questions:

<table>
<thead>
<tr>
<th>Abstract</th>
<th>The method section was revised to describe the method and primary outcomes.</th>
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<tbody>
<tr>
<td>1. Methods not clear. No methods described, and no primary outcomes described.</td>
<td>In a controlled trial on PITC (Cape Town, 2007), we compared HIV follow-up care for a nested cohort of 930 HIV-positive patients. We cross-referenced HIV testing and laboratory records to determine access to CD4 and viral load testing as primary outcomes.</td>
</tr>
<tr>
<td>2. “linked to CD4 testing” not clear. Does that mean provided blood sample or known returned and received results?</td>
<td>This has now been clarified in the text, by explaining that “linked to CD4 testing” means that there was a documented record of a CD4 test:</td>
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<tr>
<td></td>
<td>There was no difference in the main outcomes of patients with a record of CD4 testing (69.9% in the intervention, 65.2% in control sites, OR 0.82 (CI: 0.44-1.51; p=0.526) and viral load testing (14.9% intervention versus 10.9% in control arm; OR 0.69 (CI: 0.42-1.12; p=0.131).</td>
</tr>
<tr>
<td>3. In the conclusion, the shorten time for VL testing for ART-eligible patients is only if they were first successfully linked to care and initiated treatment?</td>
<td>That is correct. To clarify this, we expanded the explanation of who was considered ‘ART-eligible’ in the Results section of the paper, which now reads:</td>
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<td></td>
<td>In the intervention arm, patients found to be ART-eligible based on their CD4 test result, accessed viral load testing approximately 2.5 months sooner than those in the control arm (214 days vs. 288 days, HR: 0.417, 95% CI: 0.221 to 0.784; p = 0.007).</td>
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</table>

**Background**

P 4, paragraph 2, sentence 2: Why would testing situation alter access to treatment? Regardless of

To clarify, we added further explanation to this sentence which now reads:

Claims that PITC may be able to increase access to earlier diagnosis and care compared to other testing approaches (through, for
 Instance, integrating HIV testing into standard clinical care), are still unsubstantiated [10, 13].

Under the study design, pg.8 we commented on this as follows:

The study hypothesised that the PITC intervention would offer more opportunity for linkage to care compared to the VCT option (due to the closer, routine involvement of clinical staff in the HIV testing process).

And on pg. 9

For the PITC approach, STI nurses offered HIV testing in the STI consultation and it was thought that this would be more advantageous for linking patients to care. For instance, the clinical consult allowed nurses to more easily request a CD4 test blood test on the same day and to encourage patients to return for a follow-up visit to receive their CD4 test result together with their other STI test results.

This issue is also addressed in the Discussion section, on pg.16:

One suggestion is that the closer involvement of nurses with the process of HIV testing within the clinical STI consultation, may have allowed nurses to more easily inform patients of the medical benefits of seeking immediate referral for ART initiation. Also, all STI patients are asked to return for a follow-up visit to receive their syphilis test result, so this could have provided patients with a ready-made opportunity to return to receive their CD4 test result and for timely referral for ART initiation.

And on pg.19 (the paragraph before the Strengths and limitations section) where the authors make recommendations about how best the PITC approach can improve linkage to HIV care in this setting.

<table>
<thead>
<tr>
<th>P 4, para 1, sentence 3: You could add the two references in this sentence. You do it later, but it seems they could belong here.</th>
<th>This comment is about adding references to sentence 3, and we were unclear what references the reviewer was referring to. Given that sentence 3 is already referenced and that we were unclear about this recommendation, we were unfortunately not able to respond to this comment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 5. Figure 1 is pretty generic and not needed.</td>
<td>Figure 1 was removed and all references to Figure 1 was removed from the manuscript.</td>
</tr>
</tbody>
</table>
| P 6. So the focus is linkage from HIV testing to CD4 testing (staging) and then staging to initiation (proxy | Patients who did not have CD4 test record, were not followed up. Viral load records were searched for all patients with a CD4 records, whether ART-eligible or not. However, as explained in Point 3 above, we did not look for follow-up CD4 tests for those patients who were
by viral load test) for those ART-eligible. What about patients staged who were not ART eligible?

not yet eligible for initiation onto ART and we acknowledge that this is a gap in our investigation and it could have strengthened the study. As mentioned in our response to point 3 above, we made a recommendation that this be considered in further research.

P 6. I would check on the clinical guidelines. I doubt CD4 testing without any clinical exam is consistent with guidelines

This statement has been corrected in the text (pg.5, last prg.) to read: 
‘CD4 testing and clinical examination’

P 7. Using CD4 lab results as a proxy for linkage to care is problematic because you do not know if a patient ever returned to receive their results. In the STI clinic, once a person was diagnosed with HIV, was a blood sample taken for CD4 testing at that time or did they have to come back for another visit? Even if the patient does not return for their CD4 result, the result will exist in the NHLS database.

We acknowledge that using CD4 lab results as a proxy for linkage to care is limited as an indicator. We addressed this in Point 2 above. In the STI clinics, at the time of the study, there was no standard practice for drawing blood for CD4 testing on the day of HIV diagnosis, partly because HIV testing and clinical services were not fully integrated and in the case of the new PITC intervention, this was not specified as a requirement of the intervention. It would appear from the results of this study, that in fact, most STI patients had blood drawn for CD4 testing on the same day or within less than a week of their STI visit in both the intervention and control arms. In the PITC arm, based on observation of clinical consultations, STI patients were often asked to return to receive their CD4 test result (or sometimes to have blood drawn for a CD4 test), when they were scheduled to receive their VDRL test result, typically a week to 10 days after their STI visit. Under Study design (pg 7-8), we acknowledge this limitation.

Access to these tests was used as a proxy for whether patients received the appropriate type of care, though it is acknowledged that this is not a comprehensive indicator of linkage to care. The existence of a laboratory test record does not indicate that the patient returned and was informed of the test result and this is noted as a limitation in the Discussion section.

An in the discussion section, pg .15 we added a sentence to this effect:

Most CD4 tests in both arms were done within less than a week of HIV testing and this, together with the relatively high level of CD4 tests done, point to a strength of the health service in terms of ensuring that appropriate blood tests are done as the first stage in linkage to care. However, this indicator cannot tell us what proportion of those with CD4 test records actually returned to the clinic and was informed of the test result.

P 8. In the non-PITC sites, could a person receiving STI services receive an HIV test as part of the same interaction with a health worker, or where they referred to another person in the PHC for HIV testing?

In the non-PITC sites, a person receiving STI services typically did not receive an HIV test, unless they explicitly asked the STI nurse for an HIV test. In these sites, even if they did ask the STI nurse, and HIV test would not necessarily be done on the same day as the nurse would refer them to the parallel HIV counselling services provided by the HIV lay counsellors, usually to make an appointment for another day. This has now been clarified in Table 1 and in the text (see also our response below.)
P 8 and Table 2: It seems that the motivation for coming (seeking STI care) is the same for both groups? If so, this is not clear.  

Yes, in both control and intervention sites, patients are seeking STI care as their reason for visiting the clinic. This is now clarified in the text of in Table 2 and in the text on page 8-9 (see extract below):

The differences and similarities between the standard VCT approach and the adapted version of the PITC approach used in this study, is outlined in Table 1. In both intervention and control sites, the reason for the clinic visit is to seek treatment for STI. The difference in the PITC sites was that all STI patients would routinely be offered an HIV test as part of the STI consultation, whereas in the control sites, patients would not automatically be offered HIV testing in STI consultation. In the control sites, there was no standardised requirement for the clinician to raise the issue of HIV testing in the STI consultation, and in most cases, patients in control sites would only be referred to the HIV testing and counselling services, based on medical reasons (medical referral), such as the presence of HIV-related symptoms. Such patients would usually make a separate appointment for HIV testing and counselling with lay health counsellors, or they may choose to ignore the medical referral.

Also, the table of line 1 in Table 1 was changed to improve clarity.

P 9, study population: check out the spelling of hypothesised...

Spelling now corrected to ‘hypothesised’

P 9, data collection: It is not clear why you did not have the same follow up period for each person after HIV testing for CD4 testing. Having follow up between 6-12 months just confuses the issue. If you had study constraints, I’d say it up front otherwise this seems unnecessary.

The lack of a standard follow-up period is acknowledged as a limitation and the rationale was explained in Point 1 above. Further to our earlier explanation, we made some revisions to explain the logistical challenge of timing and data availability and our reasoning for not using a shortened, but standardised follow-up period. We further noted this as a limitation and as a recommendation (as described earlier).

The text under Data collection (pg. 11) was revised to explain the rationale an logistical challenge for not standardising the follow-up period for CD4 and on page 12, for viral load testing:

The first stage of the data collection process was to search for records of CD4 testing during a 12-month observation period from January to December 2007. We did not standardise the follow-up period due to logistical challenges. Data on CD4 lab records was not yet available beyond December 2007 to allow for standardised one year follow-up period for each patient (which would have required data to be available up to June 2008). We wanted to allow for the maximum follow-up period, rather than shortening the observation period to a standard 6 months. In effect, the observation period was between minimum 6 months and maximum of 12 months.  

P 10, last paragraph: Again

We revised the explanation for viral load testing as follows:
the difference length of follow up for patients makes the analysis more murky than needed

| The same NHLS database was searched, this time for a 24-month observation period from January 2007 and December 2008. The observation periods were not the same for each patient, for similar reasons as described above for the CD4 testing record search. The minimum potential follow-up time therefore was 18 months and the maximum was 24 months. |

| *We addressed this issue in the Strengths and limitations section on pg, 21, as follows:* |

| Nevertheless, the study design would have been strengthened if the follow-up period was standardised for all patients, even if this meant a shortened follow-observation period. The study also did not allow for assessing linkage to care for those not yet eligible for care or the rate of retention in care for ART patients. |

| P 11, first full paragraph: I am not sure 10% is a “small proportion”. Also, I also suspect they HIV tested in the past in a location where a blood sample was obtained from the patient, the CD4 test was performed, but the patient never returned to collect results. |

| *We concur that these patients had an earlier HIV positive test and may even have had a CD4 test done, but may not have returned for the CD4 result. We edited this sentence to remove the word “small’ when referring to the 10% figure.* |

| A proportion of patients (62 or 10%) who had CD4 test records after HIV testing, also had a record of CD4 testing before their HIV test date. |

| P 11, data analysis: It is not clear why you excluded patients with a CD4 result who were not YET eligible for ART. You mentioned guidelines where that they should return in 6 months for a next pre-ART care visit. A CD4 test should be done at that visit, so you’d look at their second CD4 test result (again, you’ll not know if the patient ever received the result). |

| *We agree this would have been a useful approach to the study. We addressed this concern in point 3 (pg 3) above.* |

| P 12, first sentence: Throwing variables on the right hand side of a logistic regression does not necessary adjust for ‘confounding’. The “full” model was presumably only run for the first outcome. |

| This is now cut as it refers to Table 5 which has been removed, as per the reviewer recommendation. |
You’d not have CD4 > 200 in the ART initiation analysis I’d suspect.

12: Under participants, I was surprised that the % HIV testing in the PITC arm was only about 14 percent points higher than in the VCT arm. While statistically significant, I’m not sure the difference is that exciting anyway. I know this result is not part of the current paper, but still perhaps worth a note. We concur. We had expected a larger effect size in the controlled trial and in the paper we explored the reasons for why the effect size may have been so low.

Table 3. I’m not sure Table 3 is that interesting. There are a lot of numbers, but the study is not powered at a site level anyway. Table 3 and any reference to Table 3 in the text, have been removed.

Table 4. The numbers used in each analysis should be reported to help the reader. While not that important, you could report relative risks rather than odds-ratios, but the main point is clear anyway. In Table 4 which is now re-labeled Table 3, the numbers for the denominators for the main outcomes have now been added. Please see the new Table 3. If the meaning is clear as you point out, we would prefer to remain with reporting the odds ratios.

P 13, paragraph 3: The point of the first sentence is not clear. Of the 622 HIV+ individuals with CD4 tests (you don’t know if they received their test result), you report that 12.3% had a viral load test. I want to know first the number ART eligible. From your table, a minor share of the 622 individuals was ART eligible. The majority of individuals were not eligible, as is to be expected. They are an important group to keep “in care”, but you.

This paragraph has now been revised to provide the proportions of ART-eligible patients first and then the proportions of ART-eligible patients with viral load tests. See extracts from the revised Results section of the manuscript, pg.14:

Among the patients with CD4 test records, less than one quarter of patients were ART-eligible (according to CD4 level ≤200 cells/mm$^3$), with 19% in the intervention and 21 % in the control group being ART-eligible. When considering records of viral load testing for only the ART-eligible category (CD4 ≤200 cells/mm$^3$), there was an absolute difference of 12.2% between arms in the proportion of patients who had a record of viral load test done, representing the largest difference across CD4 sub-groups (19 out of 39 or 33.3% intervention arm versus 16 out of 76 or 21.1% control arm). The numbers in these three CD4 sub-groups were, however, too small to test statistically for differences between arms.

In the pooled analysis (intervention and control groups), the proportion with viral load test records was 12.3% (irrespective of
excluded them from further analysis. In the intervention arm the proportion was higher, but this difference was not found to be statistically significant (14.9% intervention versus 10.9% in the control arm; OR 0.69 (CI: 0.42-1.12; p=0.131). Two tests were used in the cluster-level analysis and the p-values for the cluster-level analysis were not different from the p-values in the individual analysis (for CD4 test done, Rank sum p = 0.332 and Weighted t-test p= 0.447 and for viral load test done Rank sum p = 0.101 and Weighted t-test p= 0.153).

P 13. The sample sizes for the ART eligible patients are very low. I do not think Table 5 adds anything useful to the analysis and could be deleted. The Discussion around Table 5 can also be deleted.

| Table 5 and the associated discussion was removed. |

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.