

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of a repeat HIV test in pregnancy in India
AUTHORS	Joshi, Smita; Kulkarni, Vinay; Gangakhedkar, Raman; Mahajan, Uma; Shamra, Sushama; Shirole, Devendra; Chandhiok, Nomita

VERSION 1 - REVIEW

REVIEWER	Moodley, Dhayendre University of KwaZulu Natal South Africa
REVIEW RETURNED	13-Oct-2014

GENERAL COMMENTS	<p>General: This is an important study with an impressive sample size, designed to evaluate the cost-effectiveness of a repeat HIV test in pregnancy. The most significant finding from this study is the very low incidence of HIV in pregnant women which supports other studies in demonstrating a decline in the HIV epidemic in India. Unfortunately, expected outcomes of repeat testing were not realized in this study; of the 4 women (among 9097) who seroconverted only 2 women received the prescribed PMTCT intervention. As such, I am not convinced (as a policy maker) that reallocating resources to repeat testing despite other more serious health demands will be a reasonable decision.</p> <p>Major concerns (mainly methodological issues):</p> <ol style="list-style-type: none">1. Study design is cross-sectional yet certain outcome indicators are for a cohort eg. HIV status of baby at end of 18 months. (Page 7, Line 27), mums received complete PMTCT intervention etc.2. What are the indicators of "utility"? In the data analysis, (page 7) the authors intend comparing the utility and cost effectiveness of a current testing strategy with a proposed strategy.3. Please provide clear indicators of "cost-effectiveness".4. Why was only the test "costed" in the proposed repeat test strategy? Surely, women would require counselling again and nurses would have to perform the repeat test. Personnel time and costs should also be considered.5. When comparing the current strategy with the proposed repeat test strategy, I would suggest that TOTAL costs of a STRATEGY are compared ie. Proposed repeat test strategy should also include the baseline testing costs.6. How reliable is the cost effectiveness evaluation based on 2 positive outcomes?7. The study is still an important one but it cannot be used to advocate for repeat HIV testing based on these results alone.8. I would suggest that the authors focus on the incidence, risk factors (demographic characteristics) and outcomes of the current testing strategy.
-------------------------	---

REVIEWER	Lena H. Kim, MD UCSF U.S.A.
REVIEW RETURNED	17-Feb-2015

GENERAL COMMENTS	<p>I applaud the authors for their work on this very interesting study.</p> <p>1. The manuscript needs corrections of typos, grammar and syntax to improve the communication of the content to the reader. Here are some examples:</p> <ul style="list-style-type: none"> -In the introduction section, line 13, the word "the" should probably be inserted before "world". -In the sentence line 17-21, has the 38% reduction in incident pediatric infections already occurred or is that the goal? -Line 40: 61,0000 --> is it supposed to be 61,000 or 610,000? -Many of the sentences are too long and should be split into 2. <p>2. In the abstract:</p> <ul style="list-style-type: none"> -The background section could be worded more strongly. For example, rather than "likely to miss" --> "will miss". -In the methods section, you only mention the cross sectional design of the study but I think it is important to add cost-effectiveness analysis as well. <p>3. In the methods section:</p> <ul style="list-style-type: none"> -How were potential study participants identified from the various clinic sites? Chart review? -Did the study hire/train study coordinators who carried out the consents/HIV tests or did the study utilize the existing clinic staff/infrastructure to carry out the study? <p>4. In the results section:</p> <ul style="list-style-type: none"> -It was clearly stated that 9164 women were enrolled but it would be interesting to know out of how many women total? In other words, how many eligible women declined to be in the study? -In Table I, why was the cost of the 1st HIV test \$3.33 but the 2nd test only \$0.60? <p>4. In the discussion section:</p> <ul style="list-style-type: none"> -Have you considered adding a paragraph to review the existing literature on cost-effectiveness analysis of repeat HIV testing in pregnancy? There are other published studies such as a CEA of repeat testing in sub-Saharan Africa, that could be included. -The low incidence of new HIV infection during pregnancy was a limitation but on the other hand, showing that repeat HIV testing was still cost-effective even with low incidence was a strength that was well highlighted. However, the manuscript would benefit from a more detailed discussion of other strengths and weaknesses.
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer Name D Moodley

Institution and Country: University of KwaZulu Natal

South Africa

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

General: This is an important study with an impressive sample size, designed to evaluate the cost-effectiveness of a repeat HIV test in pregnancy. The most significant finding from this study is the very low incidence of HIV in pregnant women which supports other studies in demonstrating a decline in the HIV epidemic in India. Unfortunately, expected outcomes of repeat testing were not realized in this study; of the 4 women (among 9097) who seroconverted only 2 women received the prescribed

PMTCT intervention. As such, I am not convinced (as a policy maker) that reallocating resources to repeat testing despite other more serious health demands will be a reasonable decision.

We agree with the reviewer and we are also concerned about the loss-to-follow up of 2 women out of 4 detected with new HIV infections. However we feel that this opportunity to prevent HIV to the baby should not be missed as it has been shown to be cost-effective based on our study findings.

Therefore we have added following sentences in the revised draft at following places:

a) Abstract:

Conclusions: Our results warrant consideration at the national level for including second HIV test of all pregnant women in the national programme. However prior to allocation of resources for 2nd HIV test in pregnancy, appropriate strategies will have to be planned for improving compliance for prevention of MTCT of HIV and reducing loss-to-follow-up of those women detected with HIV.

b) Discussion: Page 11, last 6 lines as follows:

The weaknesses of the study include low HIV incidence and loss-to-follow up. Although we detected 4 new HIV infections in pregnant women, only 2 women completed appropriate ART for PMTCT and their babies remained HIV un-infected at the end of 18 months. Therefore prior to allocation of resources for 2nd HIV test in pregnancy, appropriate strategies will have to be planned for minimizing such loss-to-follow-up.

In addition, the issue about advocating 2nd HIV test is again elaborated in response to Q 7 and we request the reviewer to go through the same.

Major concerns (mainly methodological issues):

1. Study design is cross-sectional yet certain outcome indicators are for a cohort eg. HIV status of baby at end of 18 months. (Page 7, Line 27), mums received complete PMTCT intervention etc.

We agree with the reviewer that we have reports of the babies born to HIV-infected women and hence this is not a cross sectional study. Appropriate correction has been done at 2 places (1. Abstract: 'Methods section' 1st line and 2. page 5, last paragraph, first line).

2. What are the indicators of "utility"? In the data analysis, (page 7) the authors intend comparing the utility and cost effectiveness of a current testing strategy with a proposed strategy.

We have not addressed 'utility' in the manuscript and hence we have deleted the word 'utility' (on page 5, paragraph 2, line 7).

3. Please provide clear indicators of "cost-effectiveness".

The indicator of cost-effectiveness was program cost with addition of 2nd HIV test in pregnant women and quality-adjusted life years (QALYs) gained. This has been added on page 6, last paragraph, lines 4-5, in the sub-section 'Data analysis'.

4. Why was only the test "costed" in the proposed repeat test strategy? Surely, women would require counselling again and nurses would have to perform the repeat test. Personnel time and costs should also be considered.

In the previous submission, we had accounted for the cost of HIV test kit only for the 2nd HIV test.

However as per the reviewer's suggestion, we have revised the cost of 2nd test. Thus for 1st test as well as 2nd test, we have considered USD 3.33 each in the model. This is reflected in Figure 1 in the revised manuscript.

5. When comparing the current strategy with the proposed repeat test strategy, I would suggest that TOTAL costs of a STRATEGY are compared ie. Proposed repeat test strategy should also include the baseline testing costs.

For the proposed strategy, we have included the cost of first HIV test as well as the cost of 2nd HIV test as described above and in Figure 1.

6. How reliable is the cost effectiveness evaluation based on 2 positive outcomes?

We agree that there were only 2 positive outcomes. But we had reasonably good sample size of 9097 women included in the analysis and the cost-effectiveness analysis has taken into consideration re-testing of all 9097 and prevention of HIV in 2 babies as against no repeat testing (and the probability of HIV transmission to the baby and lifelong ART of the infected baby).

We feel that of all the biological interventions to prevent HIV transmission, PMTCT of HIV is the most efficacious intervention. If appropriate strategy of ensuring treatment of HIV-infected women and minimising loss-to-follow-up is implemented, repeat HIV testing will help in the global efforts towards eliminating HIV.

7. The study is still an important one but it cannot be used to advocate for repeat HIV testing based on these results alone.

We would like to draw the attention of the reviewer to the manuscript by Dandona L, et al (Changing cost of HIV interventions in the context of scaling-up in India. AIDS. 2008 Jul;22 Suppl 1:S43-9. doi: 10.1097/01.aids.0000327622.24232.aa) which showed that the cost of HIV testing dropped by almost half in India over 3 years as the demand increased and the number of HIV tests almost doubled. Our study has shown that it is possible to detect at least few new HIV infections in the second test in pregnant women. The logistics and referral mechanism of HIV testing of pregnant women is already in place. Pregnant women are regularly being followed-up for their antenatal visit and the feasibility of referring women for the 2nd HIV test has been evident from our study. In spite of low HIV incidence, our evaluation has shown that the proposed strategy is cost effective and provides more QALYs with less USD spent. Whereas with the current strategy, we end up spending more USD for life-long ART for HIV infected babies for less QALYs gained.

In addition, we performed sensitivity analysis with different probabilities of HIV incidence ranging from 0.0001 to 0.05 and the proposed strategy remained cost saving even with lowest and highest HIV incidence.

When the global efforts are moving towards elimination of HIV, we feel that this opportunity to prevent new HIV infections should not be missed when the risk of HIV transmission to the baby is increased in pregnancy. We agree that other factors such as loss-to-follow up should be taken into consideration prior to implementation of 2nd HIV test in pregnancy and we have added this as a recommendation in the manuscript.

8. I would suggest that the authors focus on the incidence, risk factors (demographic characteristics) and outcomes of the current testing strategy.

a) As per the reviewer's suggestion, we have added a paragraph to describe decline in HIV incidence in India on page 10, last paragraph and page 11, lines 1-8 as follows:

An important finding from this study is the low incidence of HIV in pregnant women which supports other studies in demonstrating a decline in the HIV epidemic in India. Decline in adult HIV prevalence and new HIV infections are sustained in most of the states in India including all the high prevalence states of South India and North East except for some low prevalence states(22). A report from Pune region has estimated decline in HIV incidence in young pregnant women and reported that the estimated HIV incidence decreased from 2.2/100 PYs (95% CI: 1.6 to 3.0) in 2002-2003 to 0.73/100 PYs (95% CI: 0.5 to 1.0) in 2006(23). We have previously reported 82% decline in HIV prevalence in pregnant women from 2003 to 2008 and HIV prevalence declined from 1.1% in 2003 and 0.2% in 2008(24). Our finding of HIV incidence of 0.12/ 100 PWY indicates that since 2006, during the last 8 years there appears to be substantial decline in new HIV infections among young pregnant women.

b) Since we detected only 4 new HIV infections, none of the demographic characteristics were significant.

c) Outcomes of the current strategy:

We have mentioned the outcome of current strategy in the discussion section, page 9, 1st paragraph,

lines 5-7 as follows:

Current strategy of a single HIV test results in 8.2 times more cost for less QALYs gained as compared to proposed repeat HIV testing of pregnant women. Our proposed strategy offers 1 healthy child at USD 6.8.

Reviewer Name Lena H. Kim, MD
Institution and Country UCSF
U.S.A.

1. The manuscript needs corrections of typos, grammar and syntax to improve the communication of the content to the reader. Here are some examples:

-In the introduction section, line 13, the word "the" should probably be inserted before "world".

We have tried our best to correct any typos, grammar and syntax.

-In the sentence line 17-21, has the 38% reduction in incident pediatric infections already occurred or is that the goal?

We have corrected this reference no 1 as follows:

The global plan towards elimination of new HIV infections among children has reported 38% decrease in new HIV infections among children(1).

-Line 40: 61,0000 --> is it supposed to be 61,000 or 610,000?

We have corrected the error on page 4, paragraph 2, line 6. It should have been 61,000.

-Many of the sentences are too long and should be split into 2.

We have tried our best to correct this.

2. In the abstract:

-The background section could be worded more strongly. For example, rather than "likely to miss" --> "will miss".

We have revised the sentence as follows:

Current strategy of single HIV test during pregnancy in India can miss new HIV infections acquired after the first test or those HIV infections that were missed in the first test due to a false negative HIV test.

-In the methods section, you only mention the cross sectional design of the study but I think it is important to add cost-effectiveness analysis as well.

We have added cost-effectiveness analysis in the abstract as follows:

A decision analysis model was used to evaluate cost-effectiveness of 2nd HIV test in pregnant women near term.

3. In the methods section:

-How were potential study participants identified from the various clinic sites? Chart review?

Yes, potential study participants were identified from their hospital records. We have added this in the revised manuscript on page 5, last paragraph, line 1 as follows:

Potential study participants were identified based on their antenatal chart review.

-Did the study hire/train study coordinators who carried out the consents/HIV tests or did the study utilize the existing clinic staff/infrastructure to carry out the study?

We had hired separate staff for the study purpose and this is added in revised manuscript in 'Methods' section, page 5, line 6 as follows:

Study staff was hired and trained prior to study initiation.

4. In the results section:

-It was clearly stated that 9164 women were enrolled but it would be interesting to know out of how

many women total? In other words, how many eligible women declined to be in the study?
None of the women declined HIV test and we have added this in 'Results' section, 1st paragraph, page 8, line 6-7. However it is not possible to get information about the total number of women eligible for 2nd test due to very large patient load as more than 17,000 pregnant women were tested for HIV at the study sites during the study period.

-In Table I, why was the cost of the 1st HIV test \$3.33 but the 2nd test only \$0.60?
The cost of 1st HIV test included infrastructure and manpower cost and it is USD 3.33. For the 2nd HIV test, we had considered only the HIV test kit cost that we paid and thus it was USD 0.6. This cost did not account for personnel, etc.

Following suggestions from both the reviewers, we have added USD 3.33 as the cost of 2nd HIV test. We request the reviewer to kindly refer to our response to comment no. 4 of the first reviewer.

4. In the discussion section:

-Have you considered adding a paragraph to review the existing literature on cost-effectiveness analysis of repeat HIV testing in pregnancy? There are other published studies such as a CEA of repeat testing in sub-Saharan Africa, that could be included.

We have added the reference regarding HIV rescreening in pregnant women in Africa on page 12, 1st paragraph, lines 1-5 as follows:

In addition to CDC(13), rescreening of pregnant women in the last trimester has been recommended by South African government(26). South Africa is a country with very HIV prevalence as well as HIV incidence. The cost-effectiveness of HIV re-screening during pregnancy in South Africa was shown to prevent a substantial number of infant HIV infections and save costs to the health care system(19).

-The low incidence of new HIV infection during pregnancy was a limitation but on the other hand, showing that repeat HIV testing was still cost-effective even with low incidence was a strength that was well highlighted. However, the manuscript would benefit from a more detailed discussion of other strengths and weaknesses.

We have added strengths and limitations on page 11, last paragraph as follows:

The strengths of our study include large sample size, demonstration of incident HIV infections in pregnant women who were tested HIV negative in the 1st HIV test in pregnancy and cost-effectiveness of repeat testing for HIV in pregnancy in spite of low incidence of HIV. This is probably because of substantial reduction in the cost of HIV testing as against to the cost of life-long ART if infected with HIV. The weaknesses of the study include low HIV incidence and loss-to-follow up. Although we detected 4 new HIV infections in pregnant women, only 2 women completed appropriate ART for PMTCT and their babies remained HIV un-infected at the end of 18 months. Therefore prior to allocation of resources for 2nd HIV test in pregnancy, appropriate strategies will have to be planned for minimizing such loss-to-follow-up.

VERSION 2 – REVIEW

REVIEWER	Lena Kim UCSF, USA
REVIEW RETURNED	23-Mar-2015

GENERAL COMMENTS	The authors gave thoughtful responses to the different reviewers comments and made the corresponding revisions to their manuscript.
-------------------------	---