

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	What interventions are effective in improving uptake and retention of HIV-positive pregnant and breastfeeding women and their infants in prevention of mother to child transmission care programs in low- and middle- income countries? A systematic review and meta-analysis
<b>AUTHORS</b>	Puchalski Ritchie, LM; van Lettow, Monique; Pham, Ba; Straus, Sharon; Hosseinipour, Mina C.; Rosenberg, Nora; Phiri, Sam; Landes, Megan; Cataldo, Fabian

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Alison Drake University of Washington, USA
<b>REVIEW RETURNED</b>	18-Jul-2018

<b>GENERAL COMMENTS</b>	<p>The overall objective and methods for this review are sound, but the review did not adequately summarize findings. Table 1 looks like the primary abstraction form, not a consolidated version of the study that would be more appropriate for a review. Similarly, the results in the text did not provide much interpretation/summarization, but rather just summarized individual study results. The review would be significantly improved if there were more classifications of interventions (individual/system is good, but they could be classified in other ways) and summary of take-home messages of different approaches and different outcomes. In addition, a key limitation was not mentioned (see below) and overall conclusion was impacted by this omission/recognition.</p> <p><b>Methods</b></p> <ul style="list-style-type: none"> <li>- Please include the exact search term for reproducibility and transparency. You state “treatment uptake and retention” were searched but it is not clear if this phrase was searched or if other terms that relate to this concept were searched.</li> <li>- It does not seem important to include a meta-analysis of 2 studies; perhaps just summarize each independently?</li> </ul> <p><b>Results</b></p> <ul style="list-style-type: none"> <li>- Table 1 is very dense with a lot of details; it would help if the authors could develop categories to more concisely summarize the individual studies and perhaps include another table in supplementary text to show all of the details, including participant characteristics, detailed inclusion criteria, and comprehensive description of intervention. The review should summarize the interventions more, and do more synthesis of interventions. For example, figures showing the proportion that use mHealth</li> </ul>
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	<p>technology vs peer vs counseling interventions would be helpful. This categorization would also be helpful in the table.</p> <ul style="list-style-type: none"> <li>- The participant characteristics are hard to interpret as there is so much variability; for example, there is a range in marital status from 9-99% but this is not very informative. The authors could calculate weighted averages of summary statistics based on sample size.</li> <li>- “Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance.” This statement does not help synthesize the studies reviewed; there should be more text discussing different interventions and discussing similarities and differences by strategy and/or outcome.</li> </ul> <p>Discussion</p> <ul style="list-style-type: none"> <li>- Limitations – one of the key limitations is that there are a lot of temporal changes in PMTCT programs that make it difficult to assess; even interventions that are presented may now be outdated (ie interventions on sdNVP are no longer relevant). In addition, the authors conclude that ANC/HIV integration may be an effective strategy but fail to acknowledge that this is already occurring in most PMTCT programs which is why it is not being explored as an intervention. It is currently standard of care, hence this is a weak conclusion from the study results</li> </ul>
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<b>REVIEWER</b>	Brynne Gilmore Centre for Global Health, Trinity College Dublin
<b>REVIEW RETURNED</b>	03-Sep-2018

<b>GENERAL COMMENTS</b>	<p>This was a very thorough systematic review with methods that are well explained and clear, and the paper is well-written. Congrats on all the hard work! I have several minor comments and/or suggestions that you will hopefully find helpful.</p> <p>Minor:</p> <ol style="list-style-type: none"> <li>1. Please review some of the language around HIV and AIDs. Notably in the title and used throughout is ‘HIV infected...’. I would consider rephrasing to ‘pregnant women living with HIV’. A helpful resource could be – UNAIDS Terminology Guidelines, specifically pg. 4. <a href="http://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf">http://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf</a></li> <li>2. Strengths and limitations – for the last point, clarify that it was studies included in the meta that couldn’t be assessed for publication bias (line 215 states this clearly, but should be brought into this point too).</li> <li>3. Line 224 – ‘reportedly’ to ‘reported’ I believe.</li> <li>4. Can you clarify line 232 – ‘provided by authors’. Are those from the contacted experts (line 176)?</li> <li>5. Some of your cells in table 1 have full stops at the end but most done/ (i.e. Weiss 2014).</li> <li>6. At times inconsistency in how numbers are written. From 1-9, most time give the numerical, but at times it is written out in word format. i.e. line 260</li> <li>7. Line 364 – testing at 6-10, please include ‘weeks’ for clarity</li> <li>8. Line 386 – “Risk of bias...” awkward sentence</li> <li>9. Line 417 – “There was a ...” awkward “There was no significant difference...” instead?</li> <li>10. LMICs vs. SSA. While your search included LMICs, studies were only from SSA. What does this mean for your findings? Consider bringing into your discussion, or further</li> </ol>
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	<p>acknowledging the limited studies from non SSA countries, and that your findings may not hold across different LMICs.</p> <p>11. Discussion could be expanded upon. Most of the discussion is around the methodology/study types, and the difference between your study and other SRs. Would be good to include more on what your findings mean within PMTCT, and how these may be important to the field.</p> <p>Other:</p> <ol style="list-style-type: none"> <li>1. Review BMJ Opens guidelines on abbreviations in the abstract, unsure if accepted.</li> <li>2. More of a style thing – your brackets when reporting study characteristics and specifically the EPOC categorization look like reference brackets. Could consider using square to avoid any confusion?</li> </ol> <ol style="list-style-type: none"> <li>1. Could consider having Risk of Bias Table in supplement due to quantity and length of other results tables.</li> </ol>
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<b>REVIEWER</b>	Min-Woong Sohn University of Virginia School of Medicine, USA
<b>REVIEW RETURNED</b>	17-Oct-2018

<b>GENERAL COMMENTS</b>	<p>The main issue with this paper is that it included only two studies whose results were clearly statistically significant without combining them. This means that the study needs stronger justification for conducting a meta-analysis based on these two studies. Another issue was that the meta analysis method was not clearly discussed. Heterogeneity based on I-squared was not significant, suggesting that fixed effects analysis may have been more appropriate. The choice of random effects model must therefore be more clearly justified.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1:	
<p>The overall objective and methods for this review are sound, but the review did not adequately summarize findings. Table 1 looks like the primary abstraction form, not a consolidated version of the study that would be more appropriate for a review. Similarly, the results in the text did not provide much interpretation/summarization, but rather just summarized individual study results. The review would be significantly improved if there were more classifications of interventions (individual/system is good, but they could be classified in other ways) and summary of takehome messages of different approaches and different outcomes. In addition, a key limitation was not mentioned (see below) and overall conclusion was impacted by this omission/recognition.</p>	<p>Please see individual sections below where all comments in this summary section are addressed individually.</p>
Methods	

<ul style="list-style-type: none"> <li>- Please include the exact search term for reproducibility and transparency. You state “treatment uptake and retention” were searched but it is not clear if this phrase was searched or if other terms that relate to this concept were searched.</li>   <li>- It does not seem important to include a meta-analysis of 2 studies; perhaps just summarize each independently?</li> </ul>	<ul style="list-style-type: none"> <li>- the complete list of search terms is too extensive to include within the manuscript text. The full Medline search strategy which includes all terms used for primary search term (HIV, Uptake, etc.) is included as an additional file and referenced in the last sentence of the search section, line 80-181 page 8.</li>   <li>- As the number of participants contributing to the outcome included in the meta-analysis is relatively low in one of the 2 studies (Turan), power through increased sample size is improved through conduct of the meta-analysis and precision of the estimate of the effect size therefore increased. For this reason we feel inclusion of the meta-analysis findings are of</li> </ul>
	value and helpful to knowledge users.
<p><b>Results</b></p> <ul style="list-style-type: none"> <li>- Table 1 is very dense with a lot of details; it would help if the authors could develop categories to more concisely summarize the individual studies and perhaps include another table in supplementary text to show all of the details, including participant characteristics, detailed inclusion criteria, and comprehensive description of intervention.</li> <li>- The review should summarize the interventions more, and do more synthesis of interventions. For example, figures showing the proportion that use mHealth technology vs peer vs counseling interventions would be helpful. This categorization would also be helpful in the table.</li>   <li>- The participant characteristics are hard to interpret as there is so much variability; for example, there is a range in marital status from 9-99% but this is not very informative. The authors could calculate weighted averages of summary statistics based on sample size.</li>   <li>- “Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance.” This statement does not help synthesize the studies reviewed; there should be more text discussing different interventions and discussing similarities and differences by strategy and/or outcome.</li> </ul>	<ul style="list-style-type: none"> <li>- We have reduced the detail in table 1 with changes highlighted in yellow, and added the original more detailed table 1 as a supplementary file. We have however not altered the intervention classification, as the Cochrane EPOC taxonomy was designed to aid in description and organization of interventions by grouping them based on conceptual or practical similarities ( <a href="https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/EPOC%20taxonomy%20guidance_2016%2006%2017.pdf">https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/EPOC%20taxonomy%20guidance_2016%2006%2017.pdf</a> ) and is commonly used for this purpose in systematic reviews. The taxonomy is referenced within the manuscript text should readers be interested in detailed descriptions of the categories.</li>   <li>- As above we have reduced the detail in table 1 and included the more complex original table 1 as a supplementary file.</li>   <li>- We have added a section to the results and discussion synthesizing the findings according to PMTCT outcome, see lines 445-472 pages 32 &amp; 33, and lines 501-511 page 35.</li> </ul>
Discussion	

<p>- Limitations – one of the key limitations is that there are a lot of temporal changes in PMTCT programs that make it difficult to assess; even interventions that are presented may now be outdated (ie interventions on sdNVP are no longer relevant).</p>	<p>- In keeping with our registered protocol, no restrictions were placed in the inclusion criteria based on PMTCT regimen. While PMTCT drug regimens have changed the focus of this review is on approaches to improving uptake and retention in PMTCT programs in general. We feel that lessons learned may be transferable and therefore of value to alternative drug regimens as well. Home delivery is still very common in many LMICs, such that inclusion of the finding of no effect of take home infant pmtct dosing (in the case</p>
<p>- In addition, the authors conclude that ANC/HIV integration may be an effective strategy but fail to acknowledge that this is already occurring in most PMTCT programs which is why it is not being explored as an intervention. It is currently standard of care, hence this is a weak conclusion from the study results</p>	<p>of the included study, of nevirapine) may be of value to PMTCT programming in such settings.</p> <p>- We have added the following section to the discussion section, lines 486-490, page 34, to clarify future directions given that integration of care is now more commonly employed. “However, not all studies or all outcomes in some included studies showed significant benefit with integration of ANC and HIV. Therefore, as integrated care is increasingly common future work focusing on how integration of ANC and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes is needed.”</p>
<p>Reviewer 2:</p>	

<p>1. Please review some of the language around HIV and AIDs. Notably in the title and used throughout is 'HIV infected...'. I would consider rephrasing to 'pregnant women living with HIV'. A helpful resource could be – UNAIDS Terminology Guidelines, specifically pg. 4. <a href="http://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf">http://www.unaids.org/sites/default/files/media_asset/2015_terminology_guidelines_en.pdf</a></p> <p>2. Strengths and limitations – for the last point, clarify that it was studies included in the meta that couldn't be assessed for publication bias (line 215 states this clearly, but should be brought into this point too).</p> <p>3. Line 224 – 'reportedly' to 'reported' I believe.</p> <p>4. Can you clarify line 232 – 'provided by authors'. Are those from the contacted experts (line 176)?</p>	<p>1- Thank you for this helpful reference. We have reviewed it and based on the suggestion in the guideline to use either HIV-positive or person/people living with HIV/AIDS but that the later not be abbreviated, we have elected to use the former and have changed throughout the manuscript.</p> <p>2 - This clarification has been added line 559 page 37. "Due to the small number of studies included in the meta-analysis publication bias could not be examined. "</p> <p>3- reportedly has been changed to reported, line 225, page 10.</p> <p>4- This was intended to convey that full articles were obtained from authors where studies were identified by the search but not yet published. However as the studies were identified by the database and/or hand search</p>
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<p>5. Some of your cells in table 1 have full stops at the end but most done/ (i.e. Weiss 2014).</p> <p>6. At times inconsistency in how numbers are written. From 1-9, most time give the numerical, but at times it is written out in word format. i.e. line 260</p> <p>7. Line 361 – testing at 6-10, please include ‘weeks’ for clarity</p> <p>8. Line 386 – “Risk of bias...” awkward sentence</p> <p>9. Line 417 – “There was a ...” awkward “There was no significant difference...” instead?</p> <p>10. LMICs vs. SSA. While your search included LMICs, studies were only from SSA. What does this mean for your findings? Consider bringing into your discussion, or further acknowledging the limited studies from non SSA countries, and that your findings may not hold across different LMICs.</p> <p>11. Discussion could be expanded upon. Most</p>	<p>we have removed this additional detail to improve clarify. See line 233, page 11, “A total of 29,837 articles were identified through the database and hand search.”</p> <p>5- We have reviewed the formatting in the revised table 1 to ensure consistency.</p> <p>6- This has been corrected throughout the manuscript except where the number is the first word of a sentence.</p> <p>7- this has been corrected, line 371 page 29</p> <p>8- This sentence has been amended as follows to improve clarity, line 395 page 30. “Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or unclear risk of bias. “</p> <p>9- The a has been removed, the line now reads “ There was no significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.” Lines 425-427 page 31</p> <p>10- We have added this as a limitation in the discussion section, lines 563-568 pages 37-38. “ Finally, although the EPOC search filter is designed to identify articles from all low- and middle-income countries, only articles from Sub-Saharan Africa were included in the review. Results therefore may be less generalizable to LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the evidence to date and where funding should be targeted for future research based on knowledge users needs.”</p> <p>- We have added a section to the results and</p>
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<p>of the discussion is around the methodology/study types, and the difference between your study and other SRs. Would be good to include more on what your findings mean within PMTCT, and how these may be important to the field.</p>	<p>discussion synthesizing the findings according to PMTCT outcome, see lines 445-472 pages 32-33, and lines 501-511 page 35.</p>
<p>Other:</p> <ol style="list-style-type: none"> <li>1. Review BMJ Opens guidelines on abbreviations in the abstract, unsure if accepted.</li> <li>2. More of a style thing – your brackets when reporting study characteristics and specifically the EPOC categorization look like reference brackets. Could consider using square to avoid any confusion?</li> <li>3. Could consider having Risk of Bias Table in supplement due to quantity and length of other results tables.</li> </ol>	<ol style="list-style-type: none"> <li>1 - we have reviewed BMJ open guidelines and cannot find any comment with regard to abbreviations in the abstract. However, we have reviewed several recent articles and note abbreviations frequently used in abstracts.</li> <li>2- brackets in the study characteristics have been changed to square brackets</li> <li>3- We have removed the risk of bias table (formerly table 2) from the manuscript and added it as a supplementary file.</li> </ol>
<p>Reviewer 3:</p> <p>-The main issue with this paper is that it included only two studies whose results were clearly statistically significant without combining them. This means that the study needs stronger justification for conducting a meta-analysis based on these two studies.</p> <p>-Another issue was that the meta analysis method was not clearly discussed. Heterogeneity based on I-squared was not significant, suggesting that fixed effects analysis may have been more appropriate. The choice of random effects model must therefore be more clearly justified.</p>	<p>- As the number of participants contributing to the outcome included in the meta-analysis is relatively low in one of the 2 studies (Turan), power through increased sample size is improved through conduct of the meta-analysis and precision of the estimate of the effect size therefore increased. For this reason we feel inclusion of the meta-analysis findings are of value and helpful to knowledge users.</p> <p>We have added the following section to manuscript, see lines 285-290 page 21, “ We expected variation in the implementation of integrated care of ART therapy into ANC in the two studies, conducted in clinics in Zambia and Kenya. We also expected some variation in standard care in the two settings, particularly with respect to eligibility and timing of ART initiation across the two studies both of which experienced policy changes during the course of the study. We therefore used a randomeffects meta-analysis to derive the combined</p>



	<p>effect estimate of integrated care based on theoretical grounds although the <math>I^2</math> was not significant.”</p> <p>As, the statistical heterogeneity, as measured by the <math>I^2</math> of 59%, was below the predefined threshold of 75% for significant heterogeneity. This could suggest the use of fixed-effects meta-analysis. We therefore conducted the fixed-effects model and included it as a supplementary file.</p>
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### VERSION 2 – REVIEW

<b>REVIEWER</b>	Alison L Drake University of Washington, USA
<b>REVIEW RETURNED</b>	13-Dec-2018

<b>GENERAL COMMENTS</b>	<p>The section on “Synthesis of findings according to PMTCT outcomes” would benefit from some revisions and additional detail to synthesize. It is helpful to know there are differences during pregnancy, labor/delivery, vs postpartum; but as a reader I want to know which interventions (or features of interventions) are promising vs. which ones were not effective. Rather than showing the RR ranges and significance, it would be helpful if the authors described the interventions more in the text in addition to RR and significance levels. It is difficult to follow without referencing the table to figure out what the reference/intervention is about. The level of description in the patient level interventions would be helpful to include in this section.</p> <p>Revisions on lines 486-490 : the conclusion seems inappropriate to do more research to assess integration. I think the data is strong enough that no further investigations are needed.</p>
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<b>REVIEWER</b>	Brynne Gilmore Centre for Global Health, Trinity College Dublin Ireland
<b>REVIEW RETURNED</b>	19-Dec-2018

<b>GENERAL COMMENTS</b>	<p>Thank you for your attention to the comments I raised during the first round of review.</p> <p>I feel they have been considered and addressed well. Good luck on the rest of the process!</p>

## VERSION 2 – AUTHOR RESPONSE

Reviewers Comment:	Authors Response:
Reviewer 1:	
<p>The section on “Synthesis of findings according to PMTCT outcomes” would benefit from some revisions and additional detail to synthesize. It is helpful to know there are differences during pregnancy, labor/delivery, vs postpartum; but as a reader I want to know which interventions (or features of interventions) are promising vs. which ones were not effective. Rather than showing the RR ranges and significance, it would be helpful if the authors described the interventions more in the text in addition to RR and significance levels. It is difficult to follow without referencing the table to figure out what the reference/intervention is about. The level of description in the patient level interventions would be helpful to include in this section.</p>	<p>We have added details of the interventions throughout this section, see page 32-35, lines 453-522.</p> <p>Of note, based on the detail provided and multifaceted nature of the majority of interventions, it is not possible to separate effective/ineffective features of the interventions. We have added this to the limitation section, page 39, lines 609-610.</p> <p>“ The multifaceted nature of the majority of interventions evaluated and variability in PMTCT outcomes reported, limited our ability to combine studies statistically and to separate effective/ineffective features of the interventions”</p>
<p>Revisions on lines 486-490: the conclusion seems inappropriate to do more research to assess integration. I think the data is strong enough that no further investigations are needed.</p>	<p>Although 2 of the 4 included studies employing integration found improved ART use during pregnancy, no difference or in some cases worse outcomes were noted for other PMTCT outcomes. As integration is indeed becoming common, we would argue that research to improve other PMTCT outcomes in the setting of integrated care is warranted. We have amended the findings page 36, lines 536-542 to clarify the areas of PMTCT care in need of further evaluation.</p> <p>“ However, the effects of integration on PMTCT outcomes during labor and delivery and post-delivery were less clear, with no difference found for some studies (39, 34) and for some outcomes (25), and one study finding reduced ART use during labor and delivery, and post-delivery (25). Therefore, as integrated care is increasingly common, future work focusing on how integration of maternal child health and HIV care may be optimized alone or in combination with other interventions to optimize</p>

	PMTCT outcomes beyond the antenatal period is needed.”
Reviewer 2:	
Thank you for your attention to the comments I raised during the first round of review. I feel they have been considered and addressed well. Good luck on the rest of the process!	No further revisions requested.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Alison Drake University of Washington, USA
<b>REVIEW RETURNED</b>	15-Mar-2019

<b>GENERAL COMMENTS</b>	I disagree with the authors citations stating integration can have adverse outcomes. Reference 39 states “but frequent absenteeism of staff and irregular supply of consumables interfered with healthcare facility performance for both intervention and control groups”. There were problems with integration but they were also observed in the control group so this is not evidence of integration being harmful. Also, a prior systematic review found this was a favorable approach ( <a href="https://www.who.int/bulletin/volumes/91/1/12-107003/en/">https://www.who.int/bulletin/volumes/91/1/12-107003/en/</a> ). I do not think countries or programs are interested in assessing models without integration, so I still conclude the authors should keep their review findings up to date and based on current practice.
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	I also still find that the meta-analysis part is weak and that the review reads more like a description of individual studies rather than a summary (review to summarize main point, commonalities, differences). I recognize the interventions are different but I still think there needs to be more categorization of the interventions to help the readers digest the information better as that is the purpose of the review. This would likely be a major revision.
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### VERSION 3 – AUTHOR RESPONSE

Reviewers Comment:	Authors Response:
Reviewer 1:	
<p>I disagree with the authors citations stating integration can have adverse outcomes. Reference 39 states “but frequent absenteeism of staff and irregular supply of consumables interfered with healthcare facility performance for both intervention and control groups”. There were problems with integration but they were also observed in the control group so this is not evidence of integration being harmful. Also, a prior systematic review found this was a favorable approach (<a href="https://www.who.int/bulletin/volumes/91/1/12-107003/en/">https://www.who.int/bulletin/volumes/91/1/12-107003/en/</a>). I do not think countries or programs are interested in assessing models without integration, so I still conclude the authors should keep their review findings up to date and based on current practice.</p>	<p>We respectfully disagree. The prior systematic review and meta-analysis referred to by the reviewer included 4 cohort studies, 3 of which were retrospective, with the review authors noting lack of randomized controlled trials as a limitation of their review. In contrast, our review and meta-analysis addressed this limitation by including only randomized controlled trials, and given similarly positive effects on ART use during pregnancy, further the evidence of the effectiveness of integration on ART uptake during pregnancy.</p> <p>While it is true that resource challenges likely impacted implementation, and fewer adherence reports were available beyond the antenatal period, as you note, this was true for both groups. In addition, as noted by Turan et al. , who discuss this finding at some length, theirs’ is not the first study to find higher attrition later in treatment with integration (Lambdin et al., JAIDS, 62: 5; e146-e152 ), and go on to suggest that further research is needed.</p> <p>Given the current setting where integration has become standard practice, we feel the finding of lower ART use during labor/delivery and postnatally in Turan et al. study, is an important finding, as this suggests that improvements to operationalization of integration are important to optimizing its effects beyond the antenatal period. We have therefore added the sentence below to clarify the issues with operationalization in the Turan et al. study, see lines 553-556 page 40.</p> <p>“While the findings of Turan et al. (25) occurred in the setting of resource challenges impacting implementation and relatively low numbers of adherence reports beyond the antenatal period,</p>

	<p>this was the case for both intervention and control groups. Therefore, as integrated care is now common practice future work focusing on how integration of maternal child health and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes beyond the antenatal period is needed.”</p>
<p>I also still find that the meta-analysis part is weak and that the review reads more like a description of individual studies rather than a summary (review to summarize main point, commonalities, differences).</p> <p>I recognize the interventions are different but I still think there needs to be more categorization of the interventions to help the readers digest the information better as that is the purpose of the review. This would likely be a major revision.</p>	<p>As outlined in our first round of responses to reviewers, November 2018, “ As the number of participants contributing to the outcome included in the meta-analysis is relatively low in one of the 2 studies (Turan), power through increased sample size is improved through conduct of the meta-analysis and precision of the estimate of the effect size therefore increased. For this reason we feel inclusion of the meta-analysis findings are of value and helpful to knowledge users.” However, as also mentioned, we aren’t able to conduct metaanalyses across all studies because of heterogeneity, which would make the metaanalysis difficult to interpret. As a result, we have narratively described the results by intervention and outcome.</p> <p>We agree that the variability and complexity of interventions is challenging and limits the possibility of grouping interventions, as noted in table 2 where even using the standardized EPOC classifications, the majority of studies fall under more than 1 category due to the multicomponent nature of the majority of interventions. In response to the previous second round of peer review of the manuscript that was conducted in February, we added a section grouping results according to PMTCT outcome, to provide an alternative view of the results and allow end users to review the results of potential relevance to their setting based on the stage of care where gaps are noted to be occurring within their local context. To further the utility/ease of use of this section in response to the current review, we have added table 3, which outlines interventions grouped according to PMTCT outcome to more clearly show which interventions appear promising for which outcomes, see page 26-29, line 304.</p>

I disagree with the authors citations stating integration can have adverse outcomes. Reference 39 states “but frequent absenteeism of staff and irregular supply of consumables interfered with healthcare facility performance for both intervention and control groups”. There were problems with integration but they were also observed in the control group so this is not evidence of integration being harmful. Also, a prior systematic review found this was a favorable approach (<https://www.who.int/bulletin/volumes/91/1/12-107003/en/>). I do not think countries or programs are interested in assessing models without integration, so I still conclude the authors should keep their review findings up to date and based on current practice.

We respectfully disagree. The prior systematic review and meta-analysis referred to by the reviewer included 4 cohort studies, 3 of which were retrospective, with the review authors noting lack of randomized controlled trials as a limitation of their review. In contrast, our review and meta-analysis addressed this limitation by including only randomized controlled trials, and given similarly positive effects on ART use during pregnancy, further the evidence of the effectiveness of integration on ART uptake during pregnancy.

While it is true that resource challenges likely impacted implementation, and fewer adherence reports were available beyond the antenatal period, as you note, this was true for both groups. In addition, as noted by Turan et al. , who discuss this finding at some length, theirs’ is not the first study to find higher attrition later in treatment with integration (Lambdin et al., JAIDS, 62: 5; e146-e152 ), and go on to suggest that further research is needed.

Given the current setting where integration has become standard practice, we feel the finding of lower ART use during labor/delivery and postnatally in Turan et al. study, is an important finding, as this suggests that improvements to operationalization of integration are important to optimizing its effects beyond the antenatal period. We have therefore added the sentence below to clarify the issues with operationalization in the Turan et al. study, see lines 553-556 page 40.

“While the findings of Turan et al. (25) occurred in the setting of resource challenges impacting implementation and relatively low numbers of adherence reports beyond the

	<p>antenatal period, this was the case for both intervention and control groups. Therefore, as integrated care is now common practice future work focusing on how integration of maternal child health and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes beyond the antenatal period is needed.”</p>
<p>I also still find that the meta-analysis part is weak and that the review reads more like a description of individual studies rather than a summary (review to summarize main point, commonalities, differences).</p> <p>I recognize the interventions are different but I still think there needs to be more categorization of the interventions to help the readers digest the information better as that is the purpose of the review. This would likely be a major revision.</p>	<p>As outlined in our first round of responses to reviewers, November 2018, “ As the number of participants contributing to the outcome included in the meta-analysis is relatively low in one of the 2 studies (Turan), power through increased sample size is improved through conduct of the meta-analysis and precision of the estimate of the effect size therefore increased. For this reason we feel inclusion of the meta-analysis findings are of value and helpful to knowledge users.” However, as also mentioned, we aren’t able to conduct metaanalyses across all studies because of heterogeneity, which would make the metaanalysis difficult to interpret. As a result, we have narratively described the results by intervention and outcome.</p> <p>We agree that the variability and complexity of interventions is challenging and limits the possibility of grouping interventions, as noted in table 2 where even using the standardized EPOC classifications, the majority of studies fall under more than 1 category due to the multicomponent nature of the majority of interventions. In response to the previous second round of peer review of the manuscript that was conducted in February, we added a section grouping results according to PMTCT outcome, to provide an alternative view of the results and allow end users to review the results of potential relevance to their setting based on the stage of care where gaps are noted to be occurring within their local</p>

	<p>context. To further the utility/ease of use of this section in response to the current review, we have added table 3, which outlines interventions grouped according to PMTCT outcome to more clearly show which interventions appear promising for which outcomes, see page 26-29, line 304.</p>
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