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# BMJ Open

## What interventions are effective in improving uptake and retention of HIV infected 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

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| Keywords:                     | HIV, prevention of mother to child transmission, interventions, uptake, retention  |
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Manuscripts

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3 1 **What interventions are effective in improving uptake and retention of HIV infected**  
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5 2 **pregnant and breastfeeding women and their infants in prevention of mother to child**  
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7 3 **transmission care programs in low- and middle- income countries: A systematic review and**  
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9 4 **meta-analysis**  
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**Abstract****Objective:**

This review was conducted to identify interventions effective in improving uptake and retention of HIV-infected mothers and their infants in PMTCT services in LMICs in order to inform program planning.

**Methods:**

We conducted a systematic review of studies comparing usual care to any intervention to improve uptake and retention of HIV-infected pregnant or breastfeeding women and their children from birth to 2 years of age in PMTCT services in LMICs. Twenty-two electronic databases were searched for randomized, quazi-randomized, and non-randomized controlled trials, and interrupted time series studies; reference lists of included articles were searched for relevant articles. Risk of bias was assessed using the Cochrane Effective Practice and Organisation of Care Group criteria. Random effects meta-analysis was conducted for studies reporting similar interventions and outcomes.

**Results:**

We identified 29,837 articles of which 18 studies were included in our review. Because of heterogeneity in interventions and outcome measures, only 1 meta-analysis of 2 studies and 1 outcome was conducted; we found a statistically significant increase in ART use during pregnancy for integration of HIV and antenatal care relative to standard non-integrated care (pooled AOR=2.69; 95% CI 1.25-5.78, P=0.0113). The remaining studies assessing other individual, provider, or health system interventions were synthesized narratively with small effects seen across intervention categories for both maternal and infant PMTCT outcomes based predominately on evidence with moderate to high risk of bias.

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3 **69 Conclusions:**  
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6 70 The evidence on effectiveness of interventions to improve uptake and retention of mothers and  
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8 71 infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal  
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10 72 care may improve ART use during pregnancy. Future studies to replicate promising approaches  
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12 73 are needed. Improved reporting of key methodological criteria will facilitate interpretation of  
13  
14 74 findings and improve the utility of evidence to PMTCT program planners.

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16  
17 75 **Systematic review registration:** PROSPERO-CRD42015020829  
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19 76 **Key Words:** HIV, prevention of mother to child transmission, interventions, retention, uptake  
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28  
29 **80 Strengths and Limitations of this review:**  
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- 31 81 • A comprehensive search was conducted, including grey literature sources and hand  
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33 82 searching.  
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35 83 • A broad range of intervention categories, as well as, both maternal and infant outcomes  
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37 84 from across the spectrum of the PMTCT cascade were included.  
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39 85 • Our search was limited to studies conducted in low- and middle-income countries in  
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41 86 order to increase utility of findings to LMIC PMTCT programmers  
42  
43 87 • The multifaceted nature of the interventions and variability in outcomes reported, limited  
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45 88 our ability to combine studies statistically.  
46  
47 89 • Due to the small number of included studies publication bias could not be examined.  
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3 **92 Introduction:**  
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5 93 In 2015, 150,000 new HIV infections and 110,000 HIV-related deaths occurred globally among  
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7 94 children <15 years of age, with mother to child transmission the leading cause of new HIV  
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9 95 infections among children (1,2). Despite effectiveness of prevention of mother to child  
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11 96 transmission (PMTCT) of HIV regimens (3,4), uptake of and retention in PMTCT care remains  
12  
13 97 below target in many low and middle-income countries (LMICs) (4,5,6). While progress has  
14  
15 98 been made in understanding barriers to uptake and retention of women and their infants in  
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17 99 PMTCT services (7), evidence to provide guidance to LMIC implementers and policy makers  
18  
19 100 seeking to optimize PMTCT services remains limited.  
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24 101  
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26 102 Eight systematic reviews have been conducted on strategies to optimize PMTCT. Two of these  
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28 103 reviews evaluated the effectiveness of interventions, specifically, male involvement (8) and  
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30 104 integration of services (9), to improve coverage of PMTCT services. These reviews were limited  
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32 105 by the lack of studies to provide recommendations. A third review (10) examined the effects of  
33  
34 106 integration of antenatal care with postnatal and other health services for a broad range of  
35  
36 107 maternal health outcomes in LMICs; although some PMTCT studies and outcomes were  
37  
38 108 included, this was not the focus of the review. A fourth systematic review evaluated  
39  
40 109 interventions for improving initiation of antiretroviral therapy (ART) therapy in pregnant women  
41  
42 110 (11) and found the evidence quality insufficient to support recommendations. A fifth systematic  
43  
44 111 review (12) assessed the impact of China's PMTCT cascade in improving uptake and outcomes  
45  
46 112 at various steps along the cascade; specific interventions implemented to operationalize the  
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48 113 cascade were not reported. Three systematic reviews have been published since the initiation of  
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50 114 the present review. One review evaluated non-pharmacological interventions to improve quality  
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3 115 of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of  
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5 116 included studies reported PMTCT outcomes, this was not a primary focus of the review. A  
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7 117 second review focused on postpartum retention of women in PMTCT and ART care (14). This  
8  
9 118 review focused on a limited portion of the PMTCT cascade. A third review (15) focused on  
10  
11 119 interventions to improve PMTCT service delivery and promote retention. This review included a  
12  
13 120 range of study designs and studies conducted in both high and low-middle income countries and  
14  
15 121 as such, is of less value as a guide to decision making for PMTCT policy and programming in  
16  
17 122 LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by:  
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19 123 lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade  
20  
21 124 and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high  
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23 125 income country studies where the context of PMTCT care is often substantially different than in  
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25 126 LMICs.  
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33 128 This review was developed in collaboration with knowledge users from the Malawi Ministry of  
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35 129 Health's HIV treatment and care technical working group. The objective of this current review  
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37 130 was to identify what interventions at the patient, provider, or health system level are effective  
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39 131 compared to no intervention or usual care in improving uptake and retention of HIV infected  
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41 132 mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health  
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43 133 services in LMICs, this review is targeted to provide guidance for PMTCT policy and  
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45 134 programming in LMICs, and therefore included a broad range of intervention categories, as well  
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47 135 as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.  
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3 **138 Methods:**  
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5 **139 *Protocol:*** A protocol was developed for this review based on the Cochrane Handbook for  
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8 **140** systematic reviews (16) and the Cochrane Effective Practice and Organisation of Care Group  
9  
10 **141** (EPOC) (17) and registered with PROSPERO (CRD42015020829, available at:  
11  
12 **142** [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015020829#](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020829#).  
13  
14 **143** VXHCNUZBn5I). The complete protocol was previously published and the methods are  
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16 **144** presented briefly here (18). Our findings are reported using the PRISMA statement for reporting  
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19 **145** systematic reviews (19).  
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24 **147 *Eligibility Criteria:***  
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26 **148** We included studies reporting the effectiveness of interventions in improving uptake and/or  
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28 **149** retention of HIV-infected pregnant or breast feeding women and their children from birth to 2  
29  
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31 **150** years of age or termination of breast feeding in PMTCT services. We included randomized,  
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33 **151** quasi-randomized and non-randomized controlled trials, and interrupted time series studies that  
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35 **152** compared usual care or no intervention to any type of intervention at the patient, provider, or  
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37 **153** health system level. Although included in error in the Prospero registration for our review,  
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39 **154** controlled before and after studies were not included in the protocol manuscript or search.  
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42 **155** Studies were included if conducted in LMICs as defined by the EPOC filter (20) and updated  
43  
44 **156** using the most recent World Bank World Country and Lending group classification (21). Studies  
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46 **157** that included both high and low/middle- income countries were eligible for inclusion if LMICs  
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49 **158** results could be abstracted. No restriction was placed based on language of publication,  
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51 **159** publication status, study time frame, or duration of follow-up.  
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3 161 Information Sources and Literature Search:  
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5 162 A search strategy was developed in consultation with an experienced information specialist  
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7 163 (MA) and peer reviewed by two additional information specialists (EC, BS) using the Peer  
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9 164 Review of Electronic Search Strategies checklist (22). The following databases were searched  
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11 165 from inception to July 31, 2015 and subsequently updated using the same search strategy for the  
12  
13 166 period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV,  
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15 167 pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and  
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17 168 retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global  
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19 169 Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science,  
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21 170 Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE,  
22  
23 171 ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library,  
24  
25 172 WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov.  
26  
27 173 Several databases planned for inclusion in our search were no longer available or not accessible  
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29 174 by our group at the time of the search and were therefore not included: AIDS Education Global  
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31 175 Information System, British Library Catalogue, and the New York Academy of Grey Literature.  
32  
33 176 In addition, we searched reference lists of included articles, and contacted several experts in the  
34  
35 177 field to inquire about eligible unpublished or in progress studies. See additional file for complete  
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37 178 MEDLINE search strategy.  
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47 180 Study Selection and Data Collection Process:  
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49 181 A screening checklist was developed and piloted by two authors (LPR, MvL) independently on a  
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51 182 sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement.  
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53 183 Two authors (LPR, MvL) then independently screened citations in two phases; first the titles,  
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3 184 then abstracts were screened, and second, the full-text articles were screened. Translation  
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5 185 software was utilized to screen articles at the titles and abstracts level, with no non-English  
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7 186 articles remaining at the full article review phase. A data abstraction form was created using the  
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9  
10 187 EPOC data collection form (17) and a calibration exercise done by 2 authors to ensure  
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12 188 consistency in screening and data extraction. A calibration exercise was conducted with  
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14 189 completed data extraction forms compared and discussed for each of the first three articles to  
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16 190 ensure consistency; data extraction was then completed for the remaining articles independently  
17  
18 191 and in duplicate by two authors, and discrepancies resolved by consensus (LPR, MvL).  
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20 192 Information abstracted from each study included: population, intervention, comparator, context,  
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22 193 outcomes, study design, time frame, and appropriateness of analysis (adjustment for design  
23  
24 194 effect). The primary outcomes were percentage of HIV-infected women receiving or initiated on  
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26 195 ART prophylaxis or treatment, percentage of infants born to HIV infected mothers receiving or  
27  
28 196 initiated on ART prophylaxis, and percentage of women and infants retained in PMTCT  
29  
30 197 care/completing the ART regimen as defined by the PMTCT regimen utilized (18). Secondary  
31  
32 198 outcomes included: percentage of infants completing post-exposure HIV testing 4-6 weeks after  
33  
34 199 birth and percentage of infants completing post-exposure HIV testing 6 weeks following  
35  
36 200 termination of breast feeding for all infants with known HIV exposure; percentage of HIV  
37  
38 201 exposed infants testing positive for HIV; adverse events; major or minor congenital  
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40 202 malformations; small for gestational age; pre-mature delivery; still birth; and infant death within  
41  
42 203 first two years of life (18).  
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51 204  
52 205 When necessary to clarify published data or to obtain unpublished data, we contacted primary  
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54 206 authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions,  
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3 207 and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to  
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5 208 calculate risk ratios were not available in the publication. Three responded and provided the  
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7 209 requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional  
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9 210 data as they were submitting the manuscript for publication.  
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15 212 Methodological Quality/Risk of Bias Appraisal:

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17 213 Risk of bias was assessed for each study in duplicate by two authors (LPR, MvL) using the  
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19 214 Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies  
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21 215 included in the meta-analysis, risk of publication bias could not be examined using funnel plots.  
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23 216 Selective reporting bias was assessed through review of trial registrations where available and  
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25 217 categorized as unclear if not registered.  
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31 219 Data Synthesis:

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33 220 Interventions were classified independently by two authors (LPR, MvL) using the EPOC  
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35 221 taxonomy for health system interventions and discrepancies resolved through discussion (23).  
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37 222 Clinical heterogeneity was determined based on patient, intervention, and outcome  
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39 223 characteristics. Descriptive synthesis of study results were conducted for all studies, and are  
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41 224 reportedly narratively and in tabular form. Where appropriate, random effects meta-analysis was  
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43 225 conducted to estimate intervention effects using the Metafor Package in the statistical software R  
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45 226 (24). Statistical heterogeneity was examined using the  $I^2$  statistic, with  $I^2 \geq 75\%$  indicating  
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47 227 significant heterogeneity (16).  
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230 **Results:**

231 Literature Search:

232 A total of 29,837 articles were identified through the database and hand search and provided by  
 233 authors. After duplicates were removed 21,354 titles and abstracts were screened and 95 articles  
 234 reviewed in full. Thirty-four articles representing 18 studies with 16 companion reports met  
 235 eligibility criteria (Figure 1, flow diagram).

237 Study Characteristics:

238 Study characteristics are outlined in Table 1.

239 Table 1: Characteristics of Included Studies

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| Author ; Year          | Intervention Level/Type | Study Design  | Country; Geographic Location in Country | Study Population  | Intervention  | Comparison | Intervention Classification EPOC | Number of Participants  | Participant Characteristics   | Outcomes   |
|------------------------|-------------------------|---|---|---|---|------------|----------------------------------|---|---|--|
| Ezeano<br>lue;<br>2015 | Patient                 | Mixed<br>Method<br>s<br>Includin<br>g Small<br>Cluster<br>RCT | Nigeria<br>(Enugu state)                | Churches<br>with >20<br>baptisms/yr<br>for past 3<br>yrs, 1<br>church/per<br>community<br>with<br>churches at<br>least 5 k<br>apart .<br>Self-<br>identified<br>pregnant<br>≥18 years<br>who<br>attended<br>any church<br>site; | Monthly baby<br>showers<br>offered<br>women<br>educational<br>game shows<br>(to test their<br>knowledge of<br>healthy<br>pregnancies<br>including<br>PMTCT) and<br>contact point<br>for follow-up,<br>Mama Packs<br>(for essential<br>items during<br>pregnancy)<br>and essential<br>lab tests<br>(including HIV) | Usual care | • Outreach<br>services           | Clusters (40<br>churches)<br>3002 patients<br>enrolled of<br>these, I (n =<br>41) and C (n =<br>32) tested<br>positive for<br>HIV | <ul style="list-style-type: none"> <li>• % HIV positive:<br/>2% overall</li> <li>• Maternal age<br/>(mean): (I =<br/>29.3, C = 29.7)</li> <li>• Marital status:<br/>(I = 0% divorced,<br/>93% married,<br/>0.5% separated,<br/>7% single; C =<br/>0.15% divorced,<br/>94% married,<br/>0.5% separated,<br/>5.02% single)</li> <li>• Education<br/>level: (I = 27%<br/>primary/none,<br/>58% secondary,<br/>14% tertiary; C =<br/>24%<br/>primary/none,<br/>55% secondary,<br/>20% tertiary)</li> <li>• Age at first<br/>pregnancy: (I =<br/>63% &lt;24.9, 30%<br/>25-34.9, 1% &gt;<br/>35; C = 60%<br/>&lt;24.9, 35% 25-<br/>34.9, 2% &gt; 35 )</li> <li>• Employment<br/>status: (I = 35%<br/>full-time<br/>employed, 24%<br/>part-time<br/>employed, 38%<br/>unemployed; C<br/>= 37% full-time</li> </ul> | 1) ART<br>during<br>pregnancy<br>2) Retention<br>in care at 6-<br>8 week<br>postpartum |

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|-----------------|---------|-------------|--|--|---|--|---|--|--|--|
|                 |         |             |  |  |   |  |   |  | employed, 20% part-time employed, 42% unemployed)  |  |
| Reynolds; 2010  | Patient | Cluster RCT | Kenya (Coast, Rift Valley, and Western provinces)  | Pregnant women with HIV ≥18 and at least 32 weeks gestation  | PMTCT providers trained to prepare and counsel women on how to use a take-home nevirapine infant dose. Pregnant women instructed on how to store and administer the nevirapine dose, and instructed that if they did not deliver in a health facility or were discharged before administration of nevirapine to the baby, they were to administer nevirapine within the first 72 hours. No changes to maternal care, maternal nevirapine dose administration. | Usual care                             | • Self-management<br>• Educational outreach | Clusters: (n = 10)<br>Patients: I (n = 116 total), C (n = 87 total)  | <ul style="list-style-type: none"> <li>• Maternal age (mean): (I = 27.4, C = 28.4)</li> <li>• Marital status: (I = 7% divorced/separated/widowed, 81% married/living as married, 12% single; C = 13% divorced/separated/widowed, 81% married/living as married, 5% single)</li> <li>• Education level: (I = 16% none, 58% primary, 19% secondary, 7% post-secondary; C = 19% none, 51% primary, 25% secondary, 5% post-secondary)</li> <li>• Employment status (I = 76% unemployed, 7% salaried/hourly, 15% income based on sales/self-determined; C = 76% unemployed, 9% salaried/hourly, 15% income based on sales/self-determined)</li> </ul> | Infant ART prophylaxis at birth  |
| Weiss; 2014     | Patient | RCT         | South Africa (Gert Sibande and Nkangala districts) | HIV infected pregnant women, 24 to 30 weeks gestation, and ≥18 years of age. Women recruited and asked to invite their male partner to enroll as a couple. | 4 successive weekly sessions 90-120 minutes each. Sessions employed a cognitive-behavioral approach and addressed HIV, safer sex, sexual negotiation, and PMTCT issues. Sessions were closed, structured, of gender-concordant groups limited to 10 participants, led by trained gender-matched facilitators, and conducted in ANC's.   | Time-matched health education sessions | • Group (couple) vs individual care         | Clusters: (n = 12 antenatal clinics);<br>Patients: (n = 239 couples) | <ul style="list-style-type: none"> <li>• % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive</li> <li>• Maternal age (mean): (I = 28.3; C = 28.1)</li> <li>• Education level: (I = 57% &lt; grade 12, 43% grade 12 or more; C = 50% &lt; grade 12, 51% grade 12 or more)</li> <li>• Employment status: (I = 27% employed, 74% unemployed; C = 30% employed, 70% unemployed)</li> </ul>   | 1) ART detected in mother blood samples at birth<br>2) ART detected in infants blood at birth<br>3) Infant HIV infection rate at 6 weeks |
| Yotiebing; 2016 | Patient | RCT         | Democratic Republic of Congo                       | Newly diagnosed HIV-infected   | Participants received   | Usual care                             | • Conditional cash transfer                 | 433 women  | • Maternal age (median:IQR): I=  | 1) Retention in care at 6 weeks  |

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|               |                   |             | (Kinshasa)                   | women, <=32 weeks gestation, registering for ANC at 89 clinics in Kinshasa   | small, escalating cash payments, starting at US \$5 and increasing by \$1 each visit, on the condition that they attended scheduled clinic appointments and completed recommended actions. Incentive reset to its original value (\$5) if mother failed to complete any of the actions required at a specific visit. Maximum participant could receive through six months postpartum was \$45.          |            |   |  | 29.5 (26-34), C = 29.0 (25.0-34.0)<br>• Marital status: (I = 82.8% married/cohabitating, 17.2% divorced/separated/widow/never married; C = 82.9% married, 17.1% divorced/separated/widow/never married)<br>• Education level (median): I = 10.0 (8.0-12.0); C = 10.0 (8.0-12.0)             | postpartum<br>2) Uptake of PMTCT services through to 6 weeks postpartum<br>3) Infant HIV infection rates at 6 weeks  |
| Richter, 2014 | Patient/ Provider | Cluster RCT | South Africa (KwaZulu-Natal) | Community or primary healthcare clinics, providing both antenatal and postnatal services onsite, with annual caseload of at least 300 pregnant women, and near research center. Patients ≥18 at the time of first assessment, <34 weeks pregnant at intake, HIV infected, and enrolled in the PMTCT programme at 1 of 8 study clinics, intention to reside in the area for the duration of the study | 8-session intervention conducted by peer mentors (4 antenatal, 4 postnatal) designed to support women living with HIV (WLH) through pregnancy and early motherhood. WLH who were childbearing and had good social skills were recruited as Peer Mentors. Peer Mentors trained for ~2 months prior to implementation and were certified after being observed; in-person supervision was provided weekly. | Usual care | • Role expansion or task shifting<br>• Educational meetings | Clusters: (n = 8 clinics) [1 clinic has 2 sites, so 5 intervention, 4 control]; Patients: (n = 1200) | • Maternal age, mean (SD): (I = 26.5 (5.5); C = 26.5 (5.5))<br>• Married/lives with partner (I = 118.8%, C = 23.3%)<br>• Education level: (I = 15% primary/none, 79.3% secondary, 5.7% tertiary; C = 16.5% primary/none, 80% secondary, 3.5% tertiary)<br>• Employed (I = 51.3%, C = 39.3%) | 1) ART from the 28th week of pregnancy (AZT or HAART)<br>2) ART during labor (AZT or HAART)<br>3) NVP or HAART during labor<br>4) Infant NVP at birth<br>5) AZT dispensed for infant and medicated as prescribed |
| Kieffer; 2011 | Provider          | Cluster RCT | Swaziland                    | All pregnant women presenting for delivery at participating maternity facilities   | 1-day training course provided to nurse-midwives to increase knowledge and skills in  | Usual care | • Educational meetings                                      | Clusters: (n = 6 maternity wards); Patients: (n = 2444)  | % HIV positive at enrollment: 33% overall   | NVP in cord blood  |

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|                          |                  |                        |  |   | provision of PMTCT and to enhance confidence and counseling skills.   |   |  |  |   |   |
| Dryden - Peterso n; 2015 | Provider/Syste m | Step wedge Cluster RCT | Botswana (Gaborone)                    | ART-naïve, HIV-infected Botswana women registering at antenatal clinic before 26 weeks gestation                                      | 2-hour participatory clinical staff education sessions (on protocols for CD4 testing); open-source platform permitting automated SMS to monitor/deliver CD4 results between central labs and peripheral clinics; longitudinal support for tracing women eligible for ART initiation | Usual care  | • The use of information and communicatio n technology<br>• Educational meetings | Clusters (antenatal clinics): (n = 19 of 20) [1 clinic couldn't receive SMS results]; Patients: % HIV positive: 726/2502 (29.0% overall), I = 189 (47.6%) and C= 177 (44.6%) | <ul style="list-style-type: none"> <li>• Maternal age (median/quartile s): (I = 28 (25,33); C = 29(26,33))</li> <li>• Marital status: (I = 9% married, 89% single/divorced/widowed, 2% unknown; C = 10% married, 89% single/divorced/widowed, 2% unknown)</li> <li>• Education level: (I = 6% primary/none, 83% secondary, 8% university, 3% unknown; C = 9% primary/none, 73% secondary, 16% university, 1% unknown)</li> </ul>  | ART initiation by 30 wks gestation  |
| Mwapa sa; 2017           | Provider/Syste m | 3 Arm, Cluster RCT     | Malawi (Salima and Mangochi districts) | 30 primary health centers stratified for semi-urban vs. rural location HIV infected pregnant women initiated on the Option B+ regimen | MIP- integration of HIV/ANC, routine tracing<br><br>MIP + SMS, integrated HIV/ANC care, SMS sent to community health worker to trace if appointment missed  | Usual care: non-integrated care, routine tracing as for MIP | • Integration<br>• The use of information and communicatio n technology          | Clusters: (n = 30 health centers) Patients: (n = 1350 women)   | <ul style="list-style-type: none"> <li>• 1350 women (MIP = 34.1%; MIP+SMS = 36.5%; SOC = 29.3%)</li> <li>• Maternal age (median): MIP = 29.5 (25.0-33.7); MIP+SMS = 29.2 (24.8-33.3); SOC = 29.4 (24.7-33.2)</li> <li>• Marital status: (MIP = 4.3% single, 91.3% married, 1.1% widowed, 2.8% divorced, 0.4% missing; MIP+SMS = 4.3% single, 93.1% married, 0% widowed, 2.6% divorced, 0% missing; SOC = 1.5% single, 94.4% married, 0.8% widowed, 3.3% divorced, 0% missing)</li> <li>• Education level: (MIP = 31.9% none, 53.8% primary, 13.9% secondary and above, 0.4% missing; MIP+SMS = 37.1% none, 55.8% primary, 7.1% secondary and above, 0%</li> </ul> | 1) Maternal retention in care at 12 months postpartum trial data<br>2) Infant retention in care at 12 months postpartum trial data<br>3) Maternal retention in care at 12 months using MOH definitio<br>4) Infant retention in care at 12 months using MOH definition |



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| Oyeledun; 2017 | Provider/System | Cluster RCT        | Northern Nigeria (Benue and Kaduna states) | Facilities who had offered PMTCT services for more than 6 months, regularly identified >1 pregnant woman per month, provided onsite delivery and postpartum care, and had at least 2 trained community health extension workers.<br><br>HIV infected women, gestational age <= 34 weeks, who were ART naive and agreed to start lifelong ART  | QI teams established, visits by coaches and collaborative meetings   | Routine MOH support   | • Continuous quality improvement   | Clusters: (n = 32 health facilities, 6 later excluded due to low patient numbers) Patients: (n = 532 women, 21 withdrew leaving 511 in total) | <ul style="list-style-type: none"> <li>• 511 women (I = 51.7%; C = 48.3%)</li> <li>• Maternal age (median): I = 27 (23-30); C = 27 (23-30)</li> <li>• Marital status: (I = 94.7% married, 5.3% others; C = 93.5% married, 6.5% others)</li> <li>• Education level: (I = 37.5% less than secondary, 54.2% secondary, 8.3% tertiary; C = 46.6% less than secondary, 40.9% secondary, 12.6% tertiary)</li> </ul>   | <ol style="list-style-type: none"> <li>1) ART initiated within 2 week of enrolment</li> <li>2) Retention in care at 6 months</li> <li>3) Infants starting prophylaxis within 72 hours</li> <li>4) infant HIV testing at 6-10 weeks</li> </ol>   |
| Phiri; 2017    | Provider/System | 3 Arm, Cluster RCT | Malawi (SE, SW and Central West Zones)     | Facilities providing Option B+ PMTCT services, that did not have other PMTCT interventions or research activities beyond the Malawi national standard of care, and were expected to have at least 20 women eligible for Option B+ in a six month period.<br><br>Pregnant and breastfeeding women with HIV diagnosis and their infants. Up to 3 male sex partners could be enrolled per patient. | FBPS -facility-based peer support, women received SOC and met with "mentor mothers", women living with HIV who had recently completed PMTCT and were on ART. Mentor mothers provided one-on-one support at each clinic visit, led weekly clinic-based support groups, and contacted women within 1 week of a missed appointment.<br><br>CBPS- community-based peer support, women received SOC and met with "expert mothers", women living | SOC = standard of care facilities provided routine HIV care according to Malawi MOH guidelines. According to national guidelines, women who fail to attend the clinic within 60 days of a missed appointment are supposed to be traced. However, this rarely occurs in the routine program. | • Role expansion or task shifting outreach services<br>• The use of information and communication technology | Clusters: (n = 21 health centres [7 per arm]) Patients: (n = 1272 across the 3 arms, 3 women later excluded because they weren't ART naïve)   | <ul style="list-style-type: none"> <li>• 1269 women (FBPS = 33.7%, CBPS = 31.0%, SOC = 35.2%)</li> <li>• Maternal age (median across all 3 arms): 27 (IQR 22-31) included age 15-21 as youngest group</li> <li>• Marital status: FBPS: 1.2% never married, 91.8% married, 4.2% divorced, 2.1% widowed, 0.7% missing; CBPS: 2.3% never married, 92.1% married, 4.8% divorced, 0.8% widowed, 0% missing; SOC: 1.5% never married, 93.7% married, 2.7% divorced, 1.1% widowed, 0.9% missing</li> </ul> | <ol style="list-style-type: none"> <li>1) ART uptake</li> <li>2) Retained in care at 1 year:</li> <li>3) Retained in care at 2 years trial data</li> <li>4) Retained in care at 2 years MOH definition</li> <li>5) Infant HIV tested at 6 weeks</li> <li>6) Infant HIV infected at 6 weeks</li> </ol> |

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For peer review only

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|                  |                  |             |   |  | with HIV who recently completed PMTCT and were on ART. Expert mothers conducted routine home visits to provide HIV education and clinic visit reminders, and led monthly community-based support group meetings. Expert mothers obtained information about missed visits from ART providers and registers at the facility and were responsible for contacting these women in the community within 1 week of a missed scheduled clinic visit. |  |   |   |   |  |
| Tomlins on: 2014 | Prpvider /System | Cluster RCT | South Africa (Umlazi)                     | Pregnant women aged ≥17 and their newborns residing in the clusters during the recruitment period                | CHWs were trained to carry out structured home visits using motivational interviewing for breastfeeding counselling. Women were scheduled to receive 7 home-based visits: 2 during pregnancy, 1 within 48 h of delivery, during days 3–4 and 10–14, during weeks 3–4 and 7–8. Low birth weight neonates received 2 extra visits within the first week  | In control clusters, CHWs provided information and support on accessing social welfare grants and conducted three home-based visits: 1 during pregnancy and two during weeks 4–6 and 10–12 post-delivery | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Outreach services</li> </ul>                    | Clusters: (n = 30)<br>Patients: (n = 3957)          | <p>Maternal age (median): (I = 23; C = 23)</p> <p>- Marital status: (I = 87.6% single/divorced/widowed, 4.7% married, 7.7% cohabiting; C = 87.7% single/divorced/widowed, 3% married, 9.3% cohabiting)</p> <p>- Education level: (I = 0.5% none, 6.5% primary, 86.7% secondary, 6.3% tertiary; C = 0.5% none, 7% primary, 87% secondary, 5.5% tertiary)</p> | <p>1) Infant HIV testing by 6 weeks</p> <p>2) Infant HIV infection at 12 weeks</p>   |
| Aliyu; 2016      | System           | Cluster RCT | Rural north-central Nigeria (Niger State) | HIV-infected women and their infants, presenting for antenatal care or delivery who met 1 of following inclusion | Integrated package of PMTCT services that included point-of-care CD4 cell count or percentage testing, transition of decentralised   | Standard of care included health information, opt-out HIV testing, infant feeding counselling, referral for CD4 cell counts and  | <ul style="list-style-type: none"> <li>• Role expansion/task shifting</li> <li>• Integration</li> <li>• Packages of care</li> </ul> | Clusters: (n = 12 hospitals)<br>Patients: (n = 369) | <ul style="list-style-type: none"> <li>• 369 HIV positive patients eligible and assessed for ART initiation (I = 46.6%; C = 53.4%)</li> <li>• Maternal age (years): I = 26</li> </ul>   | <p>1) Maternal ART initiation</p> <p>2) Maternal-infant retention in care at 6 week postpartum</p> <p>3) Maternal-infant</p> |

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|                |        |                        |                            | criteria: unknown HIV status at time of presentation ; history of ART prophylaxis or treatment, but not receiving prophylaxis or treatment at the time of presentation ; or known HIV status but had never received treatment | PMTCT tasks to trained midwives, integrated mother and infant care services, active influential family member (male partner) participation, and community involvement (male community peer champions providing outreach, education, and linkage of male partners to key referral services) | treatment, ART prophylaxis, and early infant diagnosis. |   |  | (23–30); C = 28 (25–31)<br>• Marital status: (I = 99% married, 1% single, 1% divorced or separated, 0% missing or widowed; C = 96% married, 2% single, 1% divorced or separated, 2% widowed, 1% missing)<br>• Education level: (I = 8% started primary school, 10% completed primary school, 20% secondary school, 3% post-secondary school, 18% Qur'anic, 41% none, 0% other; C = 9% started primary school, 36% completed primary school, 26% secondary school, 4% post-secondary school, 9% Qur'anic, 16% none, 1% other)<br>• Employment status: (I = 3% employed, 23% unemployed, 1% student, 68% housewife, 5% other; C = 6% employed, 41% unemployed, 2% student, 42% housewife, 10% other) | retention in care at 12 weeks post partum  |
| Geelhoed; 2013 | System | Cluster RCT            | Mozambique (Tete province) | Public primary health facilities providing maternal child health and PMTCT services   | Reorganized services to deliver integrated consultations and services for mothers and their children up to 5 years of age.   | Usual care  | • Integration<br>• Educational meetings | Clusters: (n = 6)  | Not available  | 1) ART in labor:<br>2) Infants receiving prophylaxis within 48 hours<br>3) Infant HIV infected |
| Killam; 2010   | System | Step wedge Cluster RCT | Zambia (Lusaka)            | ART eligible pregnant women presenting at 8 public sector antenatal clinics in Lusaka   | Integration of ART care into antenatal care. Women already receiving ART at the general ART clinic were encouraged to continue receiving their services in the general ART clinic  | Usual care  | • Integration                           | Clusters: (n = 8 antenatal clinics)<br>Patients: (n = 31536) | • % HIV positive: (I = 21.8%; C = 22.2%)<br>• Maternal age (mean): (I = 27.5; C = 27.3)<br>• Marital status: (I = 88.1% married, 5.4% not married, 6.5% unknown; C = 89.1% married, 6.7% not married, 4.2% unknown)<br>• Education level: (I = 3.3% none, 79.8%  | ART initiation during pregnancy  |

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| Odeny; 2014           | System | RCT         | Kenya (Nyanza region)            | HIV infected women attending antenatal or HIV care; >=18 years of age; between 28 weeks gestation and delivery; enrolled in PMTCT; access to mobile phone | Custom-built, automated software to send and receive text messages. Sent 14 text messages, up to 8 sent during pregnancy, and weekly for first 6 weeks after delivery | Usual care | • The use of information and communication technology    | Patients: (n = 388 total)   | <ul style="list-style-type: none"> <li>• % HIV positive: 29.3% (388/1324)</li> <li>• Maternal age (mean): (I = 30.8% 18-24, 56.9% 25-34, 12.3% 35+; C = 33.7% 18-24, 57.5% 25-34, 8.8% 35+)</li> <li>• Married/with regular live-in partner: (I = 86.7%; C = 88.6%)</li> <li>• Education level: (I = 1.5% none, 59.0% primary, 32.8% secondary, 6.7% post-secondary; C = 1.6% none, 57.0% primary, 28.5% secondary, 13.0% post-secondary)</li> <li>• % first pregnancy: (I = 13.8%; C = 15.0%)</li> <li>• Employment status: (I = 17.9% employed; C = 20.2% employed)</li> </ul> | 1) Maternal postpartum clinic attendance to 8 weeks<br>2) Infant HIV testing by 8 weeks |
| Rotherham-Borus; 2014 | System | Cluster RCT | South Africa (Cape Town)         | Pregnant women >= 18 years of age from Capetown townships   | Antenatal and postnatal home visits by CHW in addition to standard clinic-based care  | Usual care | • Role expansion or task shifting<br>• Outreach services | <ul style="list-style-type: none"> <li>Clusters: (n = 26 [2 later removed due to low #s of pregnant women]); Patients: (n = 1144 eligible pregnant women)</li> <li>• Women living with HIV: (I = 149 (25.5%); C = 146 ( 26.7%))</li> <li>• Mean maternal age (SD) (I = 26.5 (5.5); C = 26.3(5.6))</li> <li>• Married/lives with partner: (I = 377 (58.5%); C = 324 ( 54.6%))</li> <li>• Mean (SD) highest education level: (I = 10.3, Primapara I = 222 (34.5%); C = 200 (33.7%))</li> <li>• Employment status: (I = 20% ever employed; C = 17.5% ever employed)</li> </ul> | 1) ART prior to labor<br>2) AZT or HAART during labor<br>3) NVP or HAART at onset of labor<br>4) Infant prophylaxis within 24 hours of birth<br>5) AZT dispensed for infant and medicated as prescribed<br>6) Infant HIV test at 6 weeks   |   |
| Rustagi; 2016         | System | Cluster RCT | Cote d'Ivoire, Kenya, Mozambique | Public and non-profit health facilities with PMTCT services in the study region in each country   | A five-step, facility-level systems analysis and improvement intervention designed to maximize effectiveness of PMTCT service   | Usual care | • Continuous quality improvement                         | Clusters: (n = 36 health facilities), 1876 patients   | <ul style="list-style-type: none"> <li>• Years of PMTCT initiation: (I = 17% before 2005, 50% 2005-2008, 22% after 2008; C = 17% before 2005, 67% 2005-2008, 17% after 2008)</li> </ul>  | 1) ART in pregnancy<br>2) Infants HIV tested by 6-8 weeks                               |

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|             |        |             |                         | within 20 kilometers from a main transport corridor, with no ongoing prospective studies or similar systems analysis and enhancement techniques being implemented                                 | delivery by improving understanding of inefficiencies  |  |  |   | <ul style="list-style-type: none"> <li>Monthly ANC visits Quintiles: I = 12% &lt;65, 18% 65 to &lt;86.9, 24% 86.9 to &lt;122.2, 29% 122.2 to &lt;185.3, 18% 185.3+; C = 28% &lt;65, 22% 65 to &lt;86.9, 17% 86.9 to &lt;122.2, 11% 122.2 to &lt;185.3, 22% 185.3+</li> </ul>   |  |
| Turan; 2015 | System | Cluster RCT | Kenya (Nyanza Province) | Pregnant HIV positive women $\geq 18$ , not enrolled in HIV care at baseline and their infants; Health facilities providing ANC, PMTCT, and HIV services with $\geq 20$ new ANC clients per month | Integrated clinics provided PMTCT and HIV care and treatment services within existing ANC services, starting prenatally and continuing until a definitive pediatric HIV diagnosis was obtained or the child reached 18 months of age. At this time, the woman and infant, if HIV infected, were referred for long-term care to the facility's HIV clinic | Nonintegrated ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women to a separate HIV clinic at the same facility |  | <ul style="list-style-type: none"> <li>Clusters: (n = 12)</li> <li>Patients: (n = 1172 HIV infected pregnant women)</li> <li>Integration</li> </ul> | <ul style="list-style-type: none"> <li>1) ART during pregnancy</li> <li>2) ART during Labor</li> <li>3) ART after birth</li> <li>4) Infant ART after birth</li> <li>5) ART use throughout all 3 PMTCT periods</li> <li>6) Infant HIV testing by 3 months</li> <li>7) Infant HIV testing at 9 months</li> <li>8) Infants HIV tested by 6 weeks</li> <li>9) Infants infected at 6 weeks</li> <li>10) Infants HIV tested by end of study (up to 12 months)</li> <li>11) Infants infected at 9 months</li> </ul> |  |

241

242 The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge

243 design, and 2 RCTs. The number of clusters ranged from six to 40, and participants across all

244 study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan

245 Africa between 2005 and 2016. Half of included studies reported multifaceted interventions

246 including 2 or more EPOC category components (9/18) and as a result several were categorized

247 at more than one intervention level: patient (4), provider (1), system (7), patient/provider (1), or

1  
2  
3 248 provider/system (5). Interventions directed all or in part to the health system level were most  
4  
5 249 common (12/18). Integration (5/18), role expansion or task shifting (5/18), outreach services  
6  
7  
8 250 (4/18), and use of information and communication technology (4/18) were the most common  
9  
10 251 EPOC intervention categories employed alone or as part of a complex intervention. All included  
11  
12 252 studies were conducted in Sub-Saharan Africa.

13  
14 253  
15  
16  
17 254 Reporting of population characteristics varied widely across studies as did outcome definitions.  
18  
19 255 Seven studies limited participation to pregnant women 17-18 years of age or older; median ages  
20  
21 256 across the studies ranged from 23 to 29.7 years. Marital status was reported in fourteen studies,  
22  
23 257 and varied widely from 9% to 99% of women who were married or had a live-in partner.  
24  
25  
26 258 Maternal education level was reported in twelve studies; 5 studies reported the majority of  
27  
28 259 women having no or primary education, 5 studies reported the majority of women having  
29  
30  
31 260 received secondary education, and, two reported mean/median years of education (10.3 years, 10  
32  
33 261 years (range 8-12years)). Maternal employment (6/18) and parity (2/18) status were reported in a  
34  
35 262 minority of studies (Table 1). No pre-specified adverse events were reported in the identified  
36  
37 263 studies.

38  
39 264  
40  
41  
42 265 Reported outcomes varied substantially across studies, with few studies within intervention  
43  
44 266 categories reporting comparable outcomes. For example, 5 studies reported interventions  
45  
46 267 employing integration alone (2) or in combination with other interventions (3), with only 1  
47  
48 268 PMTCT outcome in common among the two studies employing integration alone. The most  
49  
50  
51 269 commonly reported outcomes were maternal ART use during pregnancy and labor and delivery,  
52  
53 270 infant prophylaxis at birth, and infant HIV testing and infant HIV positive rates at 6-8 weeks.

271 Overall, findings are often mixed and effect sizes small, with many of uncertain clinical  
 272 significance.  
 273 As a result of the multifaceted nature of the majority of interventions employed, and variability  
 274 in PMTCT outcomes reported, the ability to combine results statistically was limited.

275  
 276 Methodological Quality:

277 Risk of bias was assessed using the Cochrane EPOC risk of bias criteria (17). Five of the 18  
 278 studies were appraised as low risk of bias on 3 or more (4 with 3, 1 with 4) of the 6 main criteria.  
 279 The most common issues encountered were unclear reporting of randomization (8/18) and  
 280 allocation concealment (11/18), and unclear reporting or high risk of bias due to lack of blinding  
 281 of participants/personnel (18/18) and blinding of outcome assessment (16/18) (Table 2).

282 **Table 2: Risk of Bias within included studies**

| Study                 | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting |
|-----------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|-----------------------------|
| Aliyu; 2016           | Low                        | Unclear                | High                                   | High                           | Low                     | Low                         |
| Dryden-Peterson; 2015 | Unclear                    | Low                    | High                                   | High                           | High                    | Low                         |
| Ezeanolue; 2015       | Low                        | Low                    | High                                   | Unclear                        | High                    | Low                         |
| Geelhoed; 2013        | Unclear                    | Unclear                | Unclear                                | Unclear                        | High                    | High                        |
| Kieffer; 2011         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Killam; 2010          | Unclear                    | High                   | High                                   | Unclear                        | High                    | Unclear                     |
| Mwapasa; 2017         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Low                         |
| Odeny; 2014           | Low                        | Low                    | High                                   | Unclear                        | Low                     | Unclear                     |
| Oyeledun; 2017        | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Phiri; 2017           | Unclear                    | High                   | High                                   | Low                            | Low                     | Low                         |

|                          |         |         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|---------|---------|
| Reynolds;<br>2010        | Unclear | Unclear | High    | High    | High    | Unclear |
| Richter;<br>2014         | Unclear | High    | High    | High    | High    | Low     |
| Rotheram-<br>Borus; 2014 | Unclear | Unclear | High    | High    | Unclear | Low     |
| Rustagi;<br>2016         | Low     | Unclear | Unclear | Unclear | Unclear | Low     |
| Tomlinson;<br>2014       | Low     | Unclear | High    | Low     | Low     | Low     |
| Turan; 2015              | Low     | High    | High    | High    | High    | Low     |
| Weiss; 2014              | Unclear | Unclear | Unclear | Unclear | Unclear | High    |
| Yotebieng;<br>2016       | Low     | Unclear | High    | High    | High    | High    |

283

284 Meta-analysis of Effect of Integration of care on ART use during pregnancy:

285 Two studies assessing integration of HIV and antenatal care relative to usual non-integrated care  
 286 were combined in a meta-analysis of 1,887 patients (25,26); there was increased use of ARTs  
 287 during pregnancy with integration of HIV and antenatal care compared to standard non-  
 288 integrated care, non-integrated care, (AOR=2.69; 95% CI=1.25, 5.78; P=0.0113, I<sup>2</sup>=59.26%)  
 289 (Figure 2).

290

291 Descriptive Synthesis:

292 Details of included studies (country, intervention, population characteristics, outcomes, etc.) and  
 293 outcomes are outlined in Table 1 and 3.

294

295 Table 3: Results of Included Studies

| Author:<br>Year    | Intervention<br>Level/Type | Intervention<br>Classification<br>EPOC | Intervention               | Control       | Outcomes<br>Intervention<br>Group   | Outcomes<br>Control Group   | Risk Ratio<br>(95%CI)                               | Adjusted<br>Statistic where<br>provided                 |
|--------------------|----------------------------|--|----------------------------|---------------|---|---|---|---|
| Ezeanolue;<br>2015 | Patient                    | •<br>Outreach<br>services              | Monthly<br>baby<br>showers | Usual<br>care | 1) ART during<br>pregnancy:<br>24/41 (65%)<br>2) Retention in<br>care at 6-8 week | 1) ART during<br>pregnancy:<br>12/32 (50%)<br>2) Retention in<br>care at 6-8 week | 1) 1.56 (0.93 -<br>2.62)<br>2) 0.92 (0.75-<br>1.12) | 1) AOR 2.8<br>(1.02-4.79)<br>2) AOR 0.39<br>(0.04-3.99) |



|                          |                  |  |   |   |  |   |   |  |
|--------------------------|------------------|--|---|---|--|---|---|--|
|                          |                  |  |   |   | postpartum:<br>33/41(81%)  | postpartum:<br>28/32(88%)   |   |  |
| Reynolds<br>; 2010       | Patient          | <ul style="list-style-type: none"> <li>• Self-management</li> <li>• Educational outreach</li> </ul>                          | Take home infant nevirapine dose  | Usual care                              | Infant ART prophylaxis at birth: 80/85 (94%)   | Infant ART prophylaxis at birth: 66/75 (88%)  | 1.07 (0.97-1.18)  | --   |
| Weiss;<br>2014           | Patient          | <ul style="list-style-type: none"> <li>• Group (couple) vs. individual care</li> </ul>                                       | Couples HIV risk reduction and PMTCT education sessions   | Time matched general education sessions | 1) ART detected in mother blood samples at birth: 9/12 (75%)<br>2) ART detected in infants blood at birth: 12/13 (92%)<br>3) Infant HIV positive:: 1/30 (3.3%)   | 1) ART detected in mother blood samples at birth: 16/12 (50%)<br>2) ART detected in infants blood at birth: 9/12 (75%)<br>3) Infant HIV positive: 3/39 (7.7%)   | 1) 1.50 (0.78-2.88)<br>2) 1.23 (0.86-1.77)<br>3) 0.43 (0.05-3.96)   | --   |
| Yotebieng;<br>2016       | Patient          | <ul style="list-style-type: none"> <li>• Conditional cash transfer</li> </ul>  | Cash payments for clinic attendance and acceptance of recommended services                        | Usual Care                              | 1) Retention in care at 6 weeks postpartum: 174/216 (80.6%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 146/216 (67.6%)<br>3) HIV positive infants at 6 weeks: 5/169 (3.0%)  | 1) Retention in care at 6 weeks postpartum: 157/217 (72.4%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%)<br>3) HIV positive infants at 6 weeks: 6/156 (3.9%)   | 1) 1.11(1.00-1.23)<br>2) 1.26(1.08-1.48)<br>3) 0.77(0.24-2.47)  | 1) ARD 1.13 (1.02-1.26)<br>2) ARD 1.31 (1.12-1.54)<br>3) –   |
| Richter,<br>2014         | Patient/Provider | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Educational meetings</li> </ul>          | Peer Mentor led educational meetings  | Usual Care                              | 1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%)<br>2) ART during labor (AZT or HAART): 282/377 (74.8%);<br>3) NVP or HAART during labor: 361/377 (95.8%)<br>4) Infant NVP at birth: 364/377 (96.6%)<br>5) AZT dispensed for infant and medicated as prescribed: 348/377 (92.3%) | 1) ART from the 28th week of pregnancy (AZT or HAART): 455/466 (95.5%)<br>2) ART during labor (AZT or HAART): 334/466 (71.7%)<br>3) NVP or HAART during labor: 456/466 (97.9%)<br>4) Infant NVP at birth: 451/466 (96.8%)<br>5) AZT dispensed for infant and medicated as prescribed: 374/466 | 1) 0.92 (0.89-0.96)<br>2) 1.04 (0.96-1.13)<br>3) 0.98 (0.95-1.00)<br>4) 1.00 (0.97-1.02)<br>5) 1.15 (1.09-1.21) | 1) AOR 0.44 (0.26,0.74)<br>2) AOR 1.16(0.44, 3.02)<br>3) AOR 0.53 (0.20, 1.41)<br>4) AOR 1.00 (0.36, 2.79)<br>5) AOR 2.98 (0.78,11.30) |
| Kieffer;<br>2011         | Provider         | <ul style="list-style-type: none"> <li>• Educational meetings</li> </ul>   | 1 day PMTCT training for nurses and midwives  | No additional training                  | NVP in cord blood: 373/465(80%)  | NVP in cord blood: 325/472 (69%)  | 1.17 (1.08, 1.26)   | ---  |
| Dryden-Peterson;<br>2015 | Provider/System  | <ul style="list-style-type: none"> <li>• The use of information and communication technology</li> <li>• Education</li> </ul> | Staff training in point of care CD4 testing and automated SMS results reporting to staff, support | Usual care                              | ART initiated by 30 wks gestation: 56/154 (36.4%)  | ART initiated by 30 wks gestation: 37/153 (24.2%)   | 1.50 (1.06-2.13)  | AOR 1.06 (0.53,2.13)   |

|                 |                  |  |   |   |   |  |  |   |
|-----------------|------------------|--|---|---|---|--|--|---|
|                 |                  | al meetings  | for patient tracing   |   |   |  |  |   |
| Mwapasa ; 2017  | Provider/Sy stem | <ul style="list-style-type: none"> <li>Integration of information and communication technology</li> </ul>  | <p>MIP= integration of antenatal and HIV care, routine patient tracing</p> <p>MIP+SMS integrated care and use of SMS enhanced tracing</p> | Usual non-integrated care and patient tracing | <p>1) Maternal retention in care at 12 months postpartum trial data: MIP 89/461, 19.3% MIP+SMS 115/493</p> <p>2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3% MIP+SMS 82/399, 20.1%</p> <p>3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4% MIP+SMS 332/493, 67%.</p> <p>4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4% MIP+SMS 323/399, 80.9%</p> | <p>1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7%</p> <p>2) Infant retention in care at 12 months postpartum trial data: SOC 32/300, 10.7</p> <p>3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1%</p> <p>4) Infant retention in care at 12 months using MOH definition: SOC 234/300, 78.0%</p> | <p>1) MIP vs SOC 0.85 (0.65-1.10), MIP+SMS vs SOC 1.03 (0.81-1.31)</p> <p>2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82)</p> <p>3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06)</p> <p>4) MIP vs SOC 0.97 (0.89-1.05), MIP+SMS vs SOC 1.04(0.96-1.12)</p> | <p>1) MIP vs SOC ARR 0.85 (0.56-1.30), MIP+SMS vs SOC ARR 1.08 (0.87-1.35)</p> <p>2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31)</p> <p>3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05)</p> <p>4) MIP vs SOC ARR 0.98 (0.89-1.09), MIP+SMS vs SOC ARR 1.01 (0.96-1.07)</p> |
| Oyeledun ; 2017 | Provider/Sy stem | <ul style="list-style-type: none"> <li>Continuous quality improvement</li> </ul>   | <p>QI teams established, coaching, and collaborative meetings</p>   | Routine MOH support                           | <p>1) ART initiated within 2 week of enrolment: 233/247 = 94.3%</p> <p>2) Retention in care at 6 months. 102/247 = 41.3%</p> <p>3) Infants starting prophylaxis within 72 hours : 138/209 = 66%</p> <p>4) Infant HIV testing at 6-10 weeks: 102/209 = 48.8%;</p>  | <p>1) ART initiated within 2 week of enrolment: 233/247 = 94.3%</p> <p>2) Retention in care at 6 months. 102/247 = 41.3%</p> <p>3) Infants starting prophylaxis within 72 hours 145/194 = 74.7%</p> <p>4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%</p>   | <p>1) 1.05 (1.01-1.08)</p> <p>2) 1.07 (0.88-1.31)</p> <p>3) 0.88 (0.78-1.00)</p> <p>4) 1.93 (1.46-2.55)</p>  | <p>1) --</p> <p>2) ARR 1.08(0.78, 1.49)</p> <p>3) ARR 0.95 (0.84, 1.07)</p> <p>4) ARR 1.76(1.27, 2.42)</p>  |
| Phiri; 2017     | Provider/Sy stem | <ul style="list-style-type: none"> <li>Role expansion or task shifting outreach services</li> <li>The use of information and communication technology</li> </ul> | <p>FBPS – facility based peer support from mentor mothers</p> <p>CBPS- community based peer support from mentor mothers</p>               | SOC- standard of care                         | <p>1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%)</p> <p>2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%)</p> <p>3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394 (54%)</p> <p>4) Retained in</p>   | <p>1) ART uptake: SOC- 361/447(81%)</p> <p>2) Retained in care at 1 year: SOC- 261/361 (74%)</p> <p>3) Retained in care at 2 years (trial data): SOC- 169/447 (38%)</p> <p>4) Retained in care at 2 years</p>  | <p>1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06- 1.18)</p> <p>2) SOC vs FBPS 1.05(0.96- 1.14), SOC vs CBPS 1.01 (0.92-1.10)</p> <p>3) SOC vs FBPS 1.38(1.19- 1.60), SOC vs CBPS 1.42</p>   | <p>1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18)</p> <p>2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20)</p> <p>3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30)</p> <p>4) --</p>  |

|                 |                 |  |  |   |  |  |   |  |
|-----------------|-----------------|--|--|---|--|--|---|--|
|                 |                 |  |  |   | care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%)<br>5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%)<br>6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%) | (MOH definition): SOC- 255/447(57%)<br><br>5) Infant HIV test at 6 weeks: SOC- 169/273(62%)<br><br>6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)   | (1.22-1.65)<br>4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43)<br>5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38)<br>6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09) | 5) --<br><br>6) ---  |
| Tomlinson: 2014 | Provider/System | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Outreach services</li> </ul>                   | 10 structured home visits from community health workers providing support in accessing social welfare grants | 3 home visits from community health workers | 1) Infant HIV testing by 6 weeks: 420/571(73.6%)<br>2) Infant HIV positive at 12 weeks: 28/568 (4.9%)  | 1) Infant HIV testing by 6 weeks: 465/698(66.6%)<br>2) Infant HIV positive at 12 weeks: 32/697 (4.6%)  | 1) 1.10 (1.03-1.19)<br>2) 1.07 (0.65-1.76)  | 1) ARR 1.10 (0.97, 1.25)<br>2) ARR 1.07 (0.69, 1.66)                   |
| Aliyu; 2016     | System          | <ul style="list-style-type: none"> <li>Role expansion /task shifting</li> <li>Integration</li> <li>Packages of care</li> </ul> | Integrated package of PMTCT services, family/male partner participation, community champions                 | Usual Care                                  | 1) Maternal ART initiation for PMTCT:166/172 (97%)<br>2) Maternal-infant retention in care at 6 weeks postpartum: 125/150 pairs (83%)<br>3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)           | 1) Maternal ART initiation for PMTCT: 77/197 (39%),<br>2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%)<br>3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%) | 1) 2.47 (2.07-2.95)<br>2) 9.44 (5.60-15.40)<br>3) 11.40 (6.40-20.34)  | 1) ARR 3.3 (1.4-7.8)<br>2) ARR 9.1 (5.2-15.9)<br>3) ARR 10.3(5.4-19.7) |
| Geelhoed ; 2013 | System          | <ul style="list-style-type: none"> <li>Integration</li> <li>Educational meetings</li> </ul>                                    | Integrated maternal child health and HIV care  | Usual Non-integrated care                   | 1) ART in labor: post intervention:112/121 (93%)<br>2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%);<br>3) Infants HIVpositive: post intervention: 9/123 (7%)                         | 1) ART in labor: intervention phase =93/96(97%)<br>2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%)<br>3) Infants HIV positive: intervention phase: 7/60(12%)               | 1) 0.96 (0.90-1.02)<br>2) 0.93 (0.88-0.97)<br>3) 0.63 (0.25-1.60)   | --<br>--<br>--   |
| Killam; 2010    | System          | <ul style="list-style-type: none"> <li>Integration</li> </ul>  | Integration of antenatal and HIV care  | Usual non-integrated care                   | ART initiation during pregnancy: 278/846 (32.9%)   | ART initiation during pregnancy: 103/716 (14.4%)   | 2.28 (1.86-2.80)  | AOR 2.01 (1.37, 2.95)  |

|                          |        |  |   |                            |  |   |   |   |
|--------------------------|--------|--|---|----------------------------|--|---|---|---|
| Odeny;<br>2014           | System | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul>        | SMS test messages during pregnancy and after delivery             | Usual care                 | <p>1) Maternal postpartum clinic attendance: 38/194 (19.6%)</p> <p>2) Infant HIV testing by 8 wks: 1172/187 (92.0%)</p>  | <p>1) Maternal postpartum clinic attendance: 22/187 (11.8%)</p> <p>2) Infant HIV testing by 8 wks: 154/181 (85.1%)</p>  | <p>1) 1.66 (1.03-2.70)</p> <p>2) 1.08 (1.00-1.16)</p>   | --  |
| Rotherham-Borus;<br>2014 | System | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Outreach services</li> </ul> | Antenatal and postnatal home visits from community health workers | Usual care                 | <p>1) ART prior to labor: 169/179 (94.4%)</p> <p>2) AZT or HAART during labor: 1164/179 (91.6%)</p> <p>3) NVP or HAART at onset of labor: 166/179 (92.7%)</p> <p>4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%)</p> <p>5) Infant ART after birth: 172/179 (96.1%)</p> <p>6) Infant HIV testing at 6 weeks: 155/160 (96.9%)</p>  | <p>1) ART prior to labor: 149/159 (93.7%)</p> <p>2) AZT or HAART during labor: 147/159 (92.5%)</p> <p>3) NVP or HAART at onset of labor: 142/159 (89.3%)</p> <p>4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%)</p> <p>5) Infant ART after birth: 142/159 (89.3%)</p> <p>6) Infant HIV testing at 6 weeks: 132/140 (94.3%)</p>  | <p>1) 1.01 (0.95-1.06)</p> <p>2) 0.99 (0.93-1.06)</p> <p>3) 1.04 (0.97-1.11)</p> <p>4) 1.08 (1.01-1.15)</p> <p>5) 1.08 (1.01-1.14)</p> <p>6) 1.03 (0.98-1.08)</p>   | <p>1) AOR 1.08 (0.42, 2.80)</p> <p>2) AOR 0.87 (0.39, 1.95)</p> <p>3) AOR 1.52(0.70, 3.31)</p> <p>4) AOR 2.94(1.41, 6.12)</p> <p>5) AOR 2.95 (1.12, 7.73)</p> <p>6) AOR 1.80 (0.62, 5.28)</p>   |
| Rustagi;<br>2016         | System | <ul style="list-style-type: none"> <li>Continuous quality improvement</li> </ul>                             | Facility level systems analysis and improvement intervention      | No-intervention            | <p>1) ART in pregnancy: 575/839 (69%)</p> <p>2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)</p>  | <p>1) ART in pregnancy: 664/1037(64%)</p> <p>2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)</p>   | <p>1) 1.07 (1.00-1.14)</p> <p>2) 1.23 (1.09-1.40)</p>   | --  |
| Turan;<br>2015           | System | <ul style="list-style-type: none"> <li>Integration</li> </ul>  | Integrated HIV and antenatal care                                 | Usual, non-integrated care | <p>1) ART during pregnancy: 138/173 (80%)</p> <p>2) ART during Labor: 28/173 (16%)</p> <p>3) ART after birth: 22/173 (13%)</p> <p>4) Infant ART after birth: 50/173 (29%)</p> <p>5) ART throughout all 3 PMTCT periods: 37/176 (21.0%)</p> <p>6) Infant HIV testing before 3 months: 143/569 (25%)</p> <p>7) Infant HIV testing at 9 months: 361/569 (63%)</p> <p>8) Infants HIV tested by 6 weeks: 143/568 (25%)</p> <p>9) Infants HIV positive at 6 weeks: 16/143 (4.2%)</p> | <p>1) ART during pregnancy: 75/152 (49%)</p> <p>2) ART during Labor: 84/152 (55%)</p> <p>3) ART after birth: 57/152 (38%)</p> <p>4) Infant ART after birth: 106/152 (70%)</p> <p>5) ART throughout all 3 PMTCT periods: 23/153 (15.0%)</p> <p>6) Infant HIV testing before 3 months: 106/603 (18%)</p> <p>7) Infant HIV testing at 9 months: 326/603 (54%)</p> <p>8) Infants HIV tested by 6 weeks: 106/594 (18%)</p> <p>9) Infants HIV positive at 6 weeks: 7/106 (6.6%)</p> | <p>1) 1.61 (1.35-1.93)</p> <p>2) 0.29 (0.20-0.42)</p> <p>3) 0.34 (0.22-0.53)</p> <p>4) 0.41 (0.32-0.54)</p> <p>5) 1.40 (0.87-2.24)</p> <p>6) 1.43 (1.14-1.79)</p> <p>7) 1.17 (1.07-1.29)</p> <p>8) 1.41 (1.13-1.76)</p> <p>9) 0.64 (0.22-1.84)</p> <p>10) 1.18 (1.08-</p> | <p>1) AOR 4.05 (2.0, 8.0)</p> <p>2) AOR 0.16 (0.04, 0.68)</p> <p>3) AOR 0.24 (0.08, 0.70)</p> <p>4) AOR 0.18 (0.09, 0.35)</p> <p>5) AOR 1.72 (0.85, 3.48)</p> <p>6) AOR 1.57 (0.61,4.07)</p> <p>7) AOR 1.47 (0.76,2.86)</p> <p>8) AOR 1.57 (0.61-4.07)</p> <p>9) AOR 0.62 (0.20,1.98)</p> <p>10) AOR 1.45 (0.71,2.82)</p> |

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|--|--|--|--|--|---|---|-------------------------------|--------------------------|
|  |  |  |  |  | 10) Infants HIV tested by end of study (up to 12 m): 382/568 (67.3%)<br>11) Infants HIV positive at 9 months: 28/382 (7.3%) | 10) Infants HIV tested by end of study (up to 12 m): 338/594 (57.0%)<br>11) Infants HIV positive at 9 months: 27/338 (8.0%) | 1.29)<br>11) 0.92 (0.55-1.53) | 11) AOR 0.89 (0.56,1.43) |
|--|--|--|--|--|---|---|-------------------------------|--------------------------|

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298 Patient Level Interventions:

299 Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of  
300 bias ranged from 3 to 6 of six criteria rated as high or unclear (Table 2). Ezeanolue et al. (27)  
301 included 40 clusters and 3,024 patients and evaluated a complex intervention that included  
302 monthly baby showers at participating churches where expectant mothers participated in  
303 educational games, received 'mama packs' containing supplies needed during delivery (sterile  
304 gloves, alcohol swabs, clean razor, etc.) and laboratory testing, and were given a contact point  
305 for follow-up. Women in the intervention group were found to be significantly more likely to  
306 complete linkage to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62];  
307 AOR=2.8 [95% CI 1.02-4.79]), but no difference was identified between groups in accessing  
308 care at 6-8 weeks postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a  
309 study that provided prepackaged syringes of infant nevirapine (NVP) doses to be given by  
310 mothers who delivered at home; no difference was found in the proportion of infants receiving  
311 NVP after delivery. Weiss et al. (29) included 12 clusters and 239 couples and evaluated a

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2  
3 312 couples'-based PMTCT intervention compared to standard care. They found no statistically  
4  
5 313 significant difference in PMTCT regimen adherence defined as ART detected in mothers blood,  
6  
7 314 ART detected in infant blood, or in the rate of infant HIV infection. Yotebieng et al. (30)  
8  
9 315 included 433 patients and evaluated whether conditional cash transfers improved adherence,  
10  
11 316 acceptance of and retention in PMTCT services to 6 weeks postpartum. They found women in  
12  
13 317 the intervention group were significantly more likely to be retained in care (RR= 1.11 [95% CI  
14  
15 318 1.00-1.23]), and to have attended all clinic visits and to have accepted recommended PMTCT  
16  
17 319 services (RR= 1.26 [95% CI 1.08-1.48]). No difference was found in infant HIV positive rates at  
18  
19 320 6 weeks.  
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26 322 Patient/Provider Level Interventions:

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28 323 One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention  
29  
30 324 directed at both patients and providers in which peer mentors were trained to provide in person  
31  
32 325 education sessions for patients. Risk of bias was rated as high or unclear on five of six criteria  
33  
34 326 (Table 2) (31). They found patients in the intervention group were significantly less likely to  
35  
36 327 adhere to ARTs during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR=  
37  
38 328 0.44 [975% CI 0.26-0.74]). No statistically significant effects were found on the remaining  
39  
40 329 outcomes including: ART use during labor and delivery, NVP or HAART during, infant NVP at  
41  
42 330 birth, and infant ART post-birth/breast feeding. Although participants were reassessed at 6 and  
43  
44 331 12 months, we were unable to reach authors for additional information on long term outcomes.  
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51 333 Provider Level Interventions:  
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3 334 Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day  
4  
5 335 PMTCT knowledge and skills training course for nurses and midwives compared to standard  
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7  
8 336 training alone (no intervention); risk of bias was rated high or unclear on five of six criteria  
9  
10 337 (Table 2). They found a statistically significant increase in the proportion of women with ART  
11  
12 338 detected in cord blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI  
13  
14 339 1.08-1.26]).  
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19 341 Provider/System Level Interventions:

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21 342 Five studies reported interventions directed at both the provider and health system level  
22  
23 343 (33,34,35,36,37). Risk of bias ranged from 2 to 5 of six criteria rated as high or unclear (Table  
24  
25 344 2). Dryden-Peterson et al. (33) included 19 clusters and 366 patients and provided staff training,  
26  
27 345 automated transmission of HIV test results to clinic staff via short message service (SMS), and  
28  
29 346 ongoing support to ante-natal clinics (i.e. education for new staff, supporting SMS printers,  
30  
31 347 monitoring and addressing clinic underperformance). There was a trend towards an increase in  
32  
33 348 the proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.  
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39  
40 350 Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess  
41  
42 351 the impact of two different patient tracing methods routine paper (MIP) and SMS triggered  
43  
44 352 tracing (MIP+SMS) combined with integrated care against standard care (SOC). They found no  
45  
46 353 significant difference in maternal retention in care at 12 months in either intervention group  
47  
48 354 relative to controls using study definitions, or ministry of health definitions for retention. They  
49  
50 355 found no statistically significant difference in infant retention in care at 12 months in either  
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3 356 intervention group relative to controls using study definitions, or ministry of health definitions  
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5 357 for retention .  
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10 359 Oyeledun et al. (35) compared a continuous quality improvement intervention including  
11  
12 360 coaching visits and collaborative meetings to standard ministry of health support in 32 clusters  
13  
14 361 and 511 patients. They found no significant difference in retention in care at 6 months, in  
15  
16 362 initiation of ART prophylaxis in infants within 72 hours of birth, or in proportion of women  
17  
18 363 initiated on ARTs within 2 weeks of enrollment. They found significantly improved rates of  
19  
20 364 infant HIV testing at 6-10 (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-2.42]).  
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24 365  
25  
26 366 Phiri et al. (36) conducted a 3-arm cluster RCT with 21 clusters and 1269 women evaluating  
27  
28 367 facility-based peer support (FBPS) and community-based peer support (CBPS) from expert  
29  
30 368 mothers against standard of care (SOC). They found non-significant improvement with FBPS  
31  
32 369 and small statistically significant improvements with CBPS in uptake of ARTs (RR= 1.12 [95%  
33  
34 370 CI 1.06-1.18]; ARD 0.09 [95% CI 0.01-0.18]), retention in care at 1 year (RR=1.01 [95% CI  
35  
36 371 0.92-1.10]; ARD= 0.08 [95% CI 0.04-0.20]), and retention in care at 2 years (RR= 1.42 [95% CI  
37  
38 372 1.22-1.65]; ARD=0.16 [95% CI 0.03-0.30]), relative to SOC. Retention in care at 2 years was  
39  
40 373 significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-  
41  
42 374 1.43]) using ministry of health definitions for retention in care. Infant HIV testing at 6 weeks was  
43  
44 375 significantly higher in the CBPS only (RR=1.23 [95% CI 1.11-1.38]). There was no difference in  
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46 376 infant HIV positive rates at 6 weeks in either intervention group.  
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3 378 Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased  
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5 379 training of community health workers and increased home visits by community health workers  
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7 380 during and post delivery to provide PMTCT counseling and newborn care. They found a  
8  
9 381 significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention  
10  
11 382 group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in  
12  
13 383 mother to child HIV transmission at 12 weeks.  
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### 19 385 System Level Interventions:

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21 386 Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias  
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23 387 ranged from 2 to 5 of six criteria rated as high or unclear risk of bias (Table 2). Aliyu et al. (38)  
24  
25 388 evaluated an integrated package of PMTCT services including point-of-care CD4 testing,  
26  
27 389 decentralized care, integrated mother/infant services, and community involvement through male  
28  
29 390 champions, compared to standard care across 12 clusters and 369 patients. They found  
30  
31 391 significant improvement in the proportion of eligible women started on ART for PMTCT (RR=  
32  
33 392 2.47 [95% CI 2.07-2.95]; ARR 3.3 [95% CI 1.4-7.8]), and in retention of mother-infant in care at  
34  
35 393 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) and 12 weeks postpartum  
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37 394 (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-19.7]).  
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44 396 Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and  
45  
46 397 evaluated the impact of integration of HIV and maternal child health services during both  
47  
48 398 antenatal and postnatal periods. They found no improvement in the proportion of women  
49  
50 399 receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48  
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52 400 hours and the proportion of HIV positive infants.  
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5 402 Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual  
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7 403 care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a  
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9  
10 404 statistically significant increase in the proportion of eligible women receiving ARTs during  
11  
12 405 pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).  
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17 407 Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during  
18  
19 408 pregnancy and post-delivery. They found statistically significant improvements in maternal  
20  
21 409 antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks  
22  
23 410 (RR= 1.08 [1.00-1.16]).  
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26 411  
27  
28 412 Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in  
29  
30 413 addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in  
31  
32 414 the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14];  
33  
34 415 AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the  
35  
36 416 intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was a  
37  
38 417 no significant difference in maternal AZT/HAART use prior to labor, during labor, maternal  
39  
40 418 NVP/HAART use at onset of labor, and infant 6 week HIV testing relative to controls.  
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47 420 Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters  
48  
49 421 in 3 countries, including 1876 patients. They found no significant improvement in the proportion  
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51 422 of pregnant women receiving ARTs.  
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3 424 Turan et al. (25) included 12 clusters and 1172 patients and examined the effects of integration  
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5 425 of HIV and antenatal care compared with standard non-integrated care. Self-reported maternal  
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7 426 ART use across the PMTCT spectrum, pre, during, and post delivery, was not significantly  
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10 427 different between groups, although it was significantly higher during pregnancy (RR=  
11  
12 428 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]). ART use was significantly lower among  
13  
14 429 intervention sites during labor delivery RR= 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00])  
15  
16 430 and post-delivery (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]). Infant ART use after  
17  
18 431 birth was significantly lower in intervention sites (RR= 0.41 [95% CI 0.32-0.54]; AOR= 0.18  
19  
20 432 [95% CI 0.09-0.35]), although infant HIV testing was increased at 6 weeks, and 9 months in  
21  
22 433 intervention sites, the difference was not statistically significant. No difference was found for  
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24 434 infant HIV infection rates at 6 weeks, or 9 months.  
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### 31 **Discussion:**

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33 437 Eighteen studies were included in our review. Heterogeneity of interventions and outcome  
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35 438 reported limited both comparison across studies and intervention categories, as well as,  
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37 439 opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias,  
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39 440 primarily due to limitations inherent to health systems research and unclear reporting of key  
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41 441 methodological factors.  
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47 443 Based on our review findings, several interventions appear promising. In the single meta-  
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49 444 analysis conducted with data from two studies (25,26), we found a significant increase in ART  
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51 445 use during pregnancy with integration of HIV and antenatal care compared to standard non-  
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53 446 integrated care. Consistent with the findings of our meta-analysis, narrative review of three  
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3 447 studies found small positive effects of integration of HIV and antenatal care, alone or as part of a  
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5 448 complex intervention, on ART use during pregnancy. Four studies evaluating different  
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7 449 approaches to outreach services alone or in combination with other interventions found small  
8  
9 450 positive effects on linkage to care, ART use during pregnancy and labor/delivery, and early  
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11 451 infant HIV testing. Two studies found positive effects of role expansion or task shifting, in the  
12  
13 452 form of peer mentorship support, on ART use during pregnancy and, when combined with  
14  
15 453 outreach services, positive effects were seen on long term retention in care and early infant HIV  
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17 454 testing. Additional strategies found to have positive effects on PMTCT outcomes, each in a  
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19 455 single study, included: educational meetings, conditional cash transfers, continuous quality  
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21 456 improvement, and use of information and communication technology.  
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28 458 In keeping with other systematic reviews focused on interventions aimed at improving PMTCT  
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30 459 care and outcomes published to date (8,9,13,14,15), our review found the evidence base available  
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32 460 to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor  
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34 461 Car et al. (9), which included a single study and found improved ART use in labor/delivery from  
35  
36 462 integration of care, our single meta-analysis including 2 studies found a positive effect of  
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38 463 integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only  
39  
40 464 2 of which met inclusion criteria for the present review, and they also found variable effects of  
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42 465 non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al.  
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44 466 (14) included 10 articles, with 2 overlapping studies included in our review, and focused on  
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46 467 postpartum retention of women in PMTCT and ART care. This latter review, which included  
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48 468 both high and LMICs and a broader range of study designs, focused on a limited portion of the  
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50 469 PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone  
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3 470 interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to  
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5 471 improve PMTCT service delivery and promote retention. Their review was conducted over a  
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7 472 similar timeframe to the present review, however, it differs from the present review in its  
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9 473 inclusion of high income country studies, inclusion of a range of study designs, and in its  
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11 474 approach to categorization of interventions. Thirty-four studies were included in their review, 11  
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13 475 of which were included in the present review. They found weak evidence for improvement of  
14  
15 476 early infant HIV diagnosis from mobile-phone based interventions and for male involvement in  
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17 477 reducing infant HIV transmission.  
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24 479 Given the focus of the present review on providing evidence-based guidance to PMTCT program  
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26 480 planners and implementers based LMICs our review differs from the reviews noted above in several  
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28 481 ways. First, to optimize the quality of evidence we limited our review to randomized and non-  
29  
30 482 randomized controlled trials and interrupted times series studies. Second, to increase the applicability of  
31  
32 483 findings to LMIC implementers, we limited our review to studies conducted in LMICs. Third, we included  
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34 484 a broad range of intervention categories and included both maternal and infant outcomes from across  
35  
36 485 the spectrum of the PMTCT cascade. Finally, in order to provide information of direct relevance to  
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38 486 implementation planning, we categorized and analyzed interventions at both the level at which they are  
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40 487 implemented (patient, provider, system) and using the EPOC intervention classification scheme, which  
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42 488 groups interventions based on the intervention process/activities employed.  
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49 Limitations:

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51 491 While agreement on data extraction was not calculated, an initial calibration exercise was carried  
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53 492 out to ensure consistency in data extraction. Following this, comparison of completed data  
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55 493 extraction forms revealed few differences. Although no study was excluded for language, it is  
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3 494 possible that use of translation software may have resulted in exclusion of an eligible study due  
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5 495 to inaccurate translation. Additionally, while unlikely to have led to a significant difference in  
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7 496 results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO  
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10 497 as the later was not accessible to the second information technologist.  
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12 498  
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14 499 The multifaceted nature of the majority of interventions evaluated and variability in PMTCT  
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16 500 outcomes reported, limited our ability to combine studies statistically. In addition, efforts to  
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18 501 contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due  
19  
20 502 to the small number of included studies publication bias could not be examined. Additionally,  
21  
22 503 although pre-specified in our protocol, interpretation of findings, most commonly infant HIV  
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24 504 infection rates, are limited by lack of power to assess secondary outcomes among included  
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26 505 studies. Finally, as 7 of the 18 studies limited participation to women 17-18 years of age or older,  
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28 506 results may be less generalizable to younger mothers.  
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35 508 *Future Directions:*  
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37 509 Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were  
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39 510 generally small and often mixed across studies, and based on a small number of studies that were  
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41 511 largely at moderate to high risk of bias. Further research is needed both to improve quantity and  
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43 512 quality of data. First, replication of promising approaches is needed. Second, improved  
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45 513 publication reporting to ensure key methodological factors are addressed and to provide detail on  
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47 514 the likely impact of factors that cannot be modified through design. This transparency in  
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49 515 reporting will enhance interpretation and utility of findings in informing PMTCT policy and  
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51 516 program decision making. For example, while the nature of designs for evaluating PMTCT  
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3 517 interventions, often make blinding of participants impossible, description of the context and  
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5 518 likely impact would aid interpretation. Additionally, use of blinded outcome assessment or  
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8 519 objective outcomes such as laboratory confirmation of ART in blood samples will increase study  
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10 520 impact. Third, given the inherent difficulties in evaluating complex interventions, increased use  
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12 521 of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would  
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14 522 be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade  
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17 523 where feasible, would allow for increased comparison across interventions.  
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## 525 **Conclusions:**

526 The body of evidence synthesized in this review and in the literature to date on effectiveness of  
527 interventions to improve uptake and retention of mothers and infants in PMTCT care is limited  
528 by low quality evidence. A single meta-analysis of 2 studies employing integration of antenatal  
529 and HIV care suggested a potential for improvement of ART use during pregnancy based on  
530 weak evidence. Overall findings are mixed and effect sizes small and of uncertain clinical  
531 significance. In order to improve the utility of evidence to program planners future studies  
532 should strive to include key outcomes across the range of the PMTCT cascade where feasible,  
533 reduce risk of bias where possible and improve reporting of key methodological factors to allow  
534 for improved assessment of risk of bias and understanding of the likely impact of risk of bias  
535 where it cannot be addressed in design.

536  
537 **List of abbreviations:** ANC: Antenatal care; ART: Anti-Retroviral Therapy; AZT: Zidovudine,  
538 EPOC: Effective Practice and Organization of Care; HAART: Highly active antiretroviral  
539 therapy, HIV: Human Immunodeficiency Virus; LMIC: Low and Middle Income Country;

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3 540 MeSH: Medical Subject Headings; MOH: Ministry of Health; NVP: Nevirapine, PMTCT:  
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5 541 Prevention of mother to child transmission of HIV; RCT: Randomized controlled trial; SMS:  
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7 542 Short message service; SOC: Standard care; Versus: vs.  
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12 544 **Declarations:**13  
14 545 **Ethics approval and consent to participate:** Not applicable.15  
16 546 **Consent for publications:** Not applicable.17  
18 547 **Availability of data and material:** Not applicable.19  
20 548 **Funding:** LPR was funded by a KT Canada Strategic Training Initiative in Health Research  
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22 549 Fellowship award in 2014. SS is funded by a Tier 1 Canada Research Chair in Knowledge  
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25  
26 551 under Grant K99 MH104154-01A1 and the National Institute of Allergies and Infectious  
27  
28 552 Diseases (P30 AI50410 and R01 AI131060-01).  
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3031  
32 553 **Competing Interests:** The authors have declared that no competing interests exist. The authors  
33  
34 554 alone are responsible for the writing and content of the paper.  
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39 556 **Authors' contributions:** LPR and MvL conceived the study. LPR and SS developed the search  
40  
41 557 strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of  
42  
43 558 article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence  
44  
45 559 tables and manuscript. LPR conducted the meta-analysis with support from BP, MCH, NER, SP,  
46  
47 560 ML, and FC provided content expertise and assisted with preparation of the protocol and  
48  
49 561 manuscript. All authors provided critical revision of the manuscript and read and approved the  
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51 562 final manuscript.  
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10 566 update, and Elise Cogo and Jessie McGowan for peer reviewing the search strategy.  
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14 568 **Patient Involvement:** No patients were involved in this study.  
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28 751  
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30 752 **Captions for appended Figures:**

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33 753 Figure 1: PRISMA diagram of search results and screening  
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35 754 Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to  
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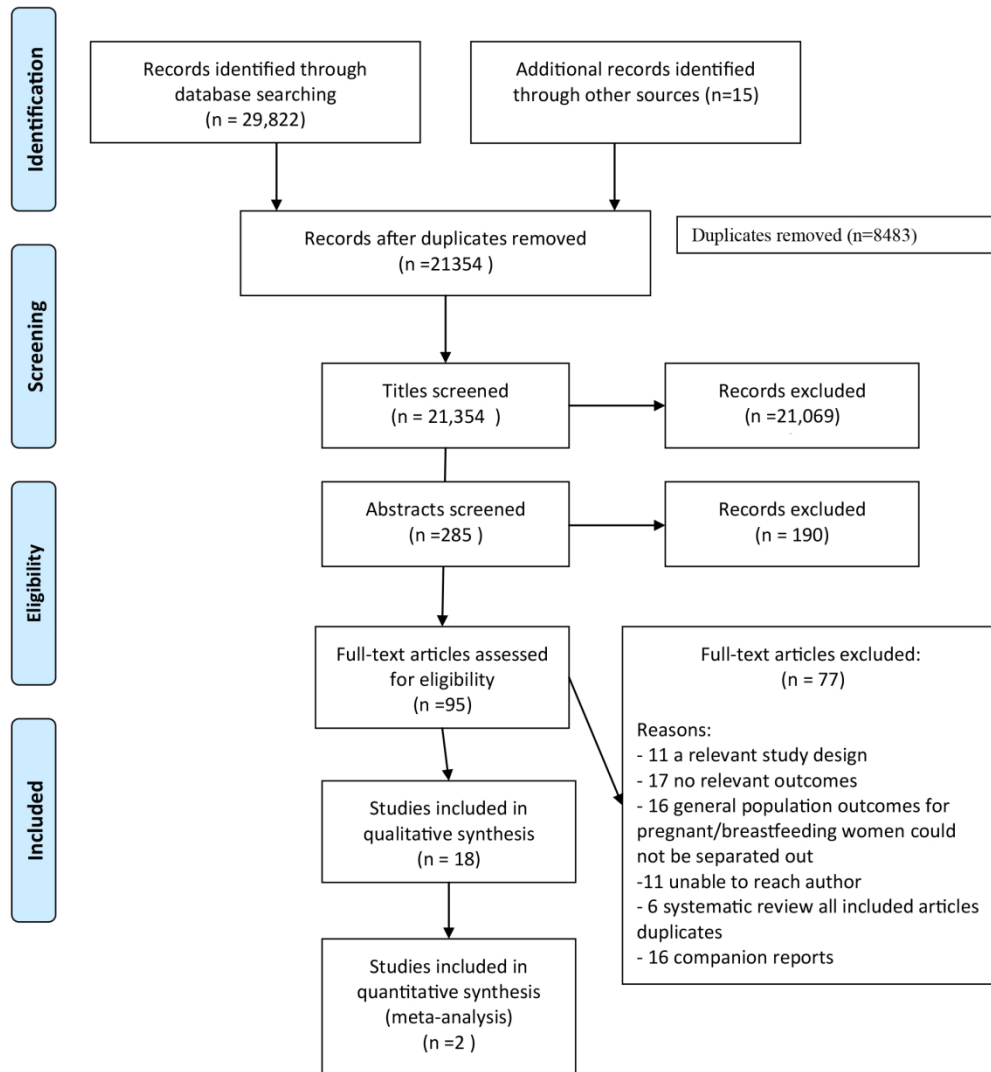


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

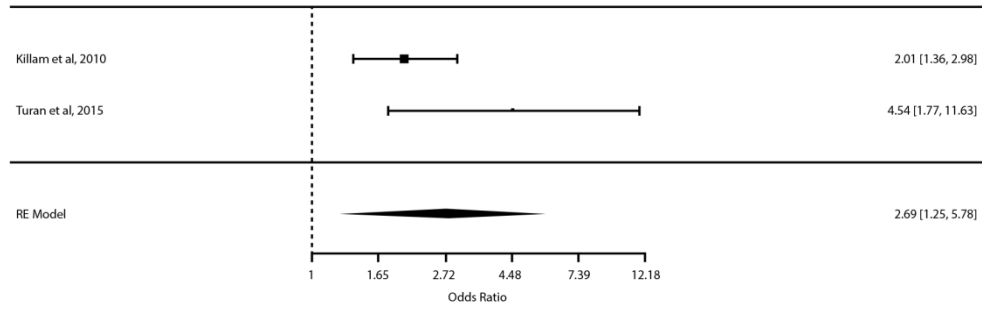


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)

## Appendix A: Search Strategy Ovid MEDLINE(R) &lt;1946 to June Week 2 2018&gt;:

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Pregnant / Breastfeeding Women

- 1 Pregnant Women/ (5226)
- 2 exp Breast Feeding/ (26666)
- 3 Milk, Human/ (15697)
- 4 Infectious Disease Transmission, Vertical/ (12256)
- 5 fetus/ (68631)
- 6 exp pregnancy/ (723003)
- 7 peripartum period/ (427)
- 8 exp Postpartum Period/ (49233)
- 9 exp pregnancy complications/ (345863)
- 10 exp Maternal Health Services/ (35913)
- 11 pregnan\*.mp,kw,kf. (778553)
- 12 gestat\*.tw,kw,kf. (144054)
- 13 breastfeed\*.mp,kw,kf. (13469)
- 14 (breast adj2 feed\*).mp,kw,kf. (30938)
- 15 (breast adj2 milk).mp,kw,kf. (8972)
- 16 breastmilk.tw,kw,kf. (683)
- 17 human milk.tw,kw,kf. (7840)
- 18 lactat\*.mp,kw,kf. (165010)
- 19 (milk adj2 eject\*).tw,kw,kf. (704)
- 20 (milk adj2 let\*-down).tw,kw,kf. (68)
- 21 ((expectant or expecting) adj2 wom#n).mp,kw,kf. (182)
- 22 parturit\*.tw,kw,kf. (11506)
- 23 birth\*.mp,kw,kf. (259925)
- 24 childbirth\*.mp,kw,kf. (14074)
- 25 child-birth\*.mp,kw,kf. (491)
- 26 deliver\*.mp,kw,kf. (474171)
- 27 puerper\*.mp,kw,kf. (21074)
- 28 breastfed.tw,kw,kf. (3524)
- 29 mtct.tw,kw,kf. (559)
- 30 pmtct.tw,kw,kf. (725)
- 31 (vertical adj2 transmission\*).tw,kw,kf. (4511)
- 32 f?etus\*.mp,kw,kf. (137278)
- 33 f?etal.mp,kw,kf. (302029)

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3 34 (breast adj2 fed\*).tw,kw,kf. (5276)  
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5 35 in-utero.tw,kw,kf. (20490)  
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7 36 (intrauterine or intra-uterine).tw,kw,kf. (42420)  
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9 37 (trans-placent\* or transplacent\*).tw,kw,kf. (5212)  
10  
11 38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)  
12  
13 39 (parent\* adj2 (child\* or infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (28605)  
14  
15 40 mother\*.tw,kw,kf. (147803)  
16  
17 41 (nursing adj2 (infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (1319)  
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19 42 (prenatal\* or pre-natal\*).tw,kw,kf. (70920)  
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21 43 (perinatal\* or peri-natal\*).tw,kw,kf. (51747)  
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23 44 (post-natal\* or postnatal\*).tw,kw,kf. (85370)  
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25 45 (antenatal\* or antenatal\*).tw,kw,kf. (23135)  
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27 46 (antepartum\* or ante-partum\*).tw,kw,kf. (4566)  
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29 47 (postpartum\* or post-partum\*).tw,kw,kf. (40829)  
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31 48 maternal\*.tw,kw,kf. (172644)  
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33 49 or/1-48 (1763167)

#### HIV/AIDS

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- 50 exp HIV Infections/ (233689)
  - 51 exp HIV/ (83825)
  - 52 HIV Long-Term Survivors/ (607)
  - 53 AIDS Serodiagnosis/ (6107)
  - 54 hiv.mp,kw,kf. (263320)
  - 55 Human T-Cell Leukemia Virus.mp,kw,kf. (2850)
  - 56 htlv-iii.mp,kw,kf. (1652)
  - 57 (acquired adj2 immun\* adj2 (syndrome\* or virus\*)).mp,kw,kf. (86030)
  - 58 (human\* adj2 immun\* adj2 deficien\* adj2 virus\*).mp,kw,kf. (491)
  - 59 (human\* adj2 immun\* adj2 virus\*).mp,kw,kf. (76929)
  - 60 (syndrome\* adj2 lymphadenopath\*).tw,kw,kf. (335)
  - 61 slim disease.tw,kw,kf. (25)
  - 62 lymphadenopathy-associated virus\*.mp,kw,kf. (295)
  - 63 lav-htlv-iii.mp,kw,kf. (211)
  - 64 sbl-6669.mp,kw,kf. (16)
  - 65 lav-2.mp,kw,kf. (25)
  - 66 (acquired adj2 immun\* adj2 deficien\* adj2 syndrome\*).tw,kw,kf. (5057)
  - 67 (aids adj10 (disease\* or syndrome\*)).mp,kw,kf. (27876)

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3 68 (aids adj1 related).tw,kw,kf. (6614)

4 69 htlv\*.tw,kw,kf. (11427)

5 70 hiv###mp,kw,kf. (1760)

6 71 or/50-70 (325026)

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10 Patient uptake / dropouts / participation

11 72 Patient Dropouts/ (6786)

12 73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)

13 74 exp Consumer Participation/ (32566)

14 75 dropout\*.tw,kw,kf. (6483)

15 76 (uptake or up-take).tw,kw,kf. (248330)

16 77 (drop\* adj1 out\$1).tw,kw,kf. (8228)

17 78 (refusal\* or refuse\$1 or refusing).tw,kw,kf. (23366)

18 79 (patient\* adj2 (elope or elope\$1 or eloping)).tw,kw,kf. (4)

19 80 (non complian\* or noncomplian\*).tw,kw,kf. (9990)

20 81 complian\*.tw,kw,kf. (84306)

21 82 (uncooperat\* or unco-operat\* or un-co-operat\*).tw,kw,kf. (1028)

22 83 (cooperat\* or co-operat\*).tw,kw,kf. (102475)

23 84 (non-accept\* or nonaccept\*).tw,kw,kf. (592)

24 85 accept\*.tw,kw,kf. (279089)

25 86 (nonparticipat\* or non-participat\*).tw,kw,kf. (1298)

26 87 participat\*.tw,kw,kf. (322007)

27 88 (nonadher\* or non-adher\*).tw,kw,kf. (10638)

28 89 adher\*.tw,kw,kf. (114637)

29 90 (retain\* or retention\*).tw,kw,kf. (244370)

30 91 (non-attend\* or nonattend\*).tw,kw,kf. (1453)

31 92 attend\*.tw,kw,kf. (110407)

32 93 (comply\* or complies or complian\*).tw,kw,kf. (91550)

33 94 (non-comply\* or noncomply\* or non-complian\* or noncomplian\*).tw,kw,kf. (10004)

34 95 reluctan\*.tw,kw,kf. (8504)

35 96 ((healthcare or care or advice or medical or information) adj3 seek\$3).tw,kw,kf. (15252)

36 97 (disengag\* or dis-engag\*).tw,kw,kf. (2812)

37 98 engag\*.tw,kw,kf. (82419)

38 99 avoid\*.tw,kw,kf. (237366)

39 100 ut.fs. (144195)

40 101 ignor\*.tw,kw,kf. (27215)

41 102 reject\*.tw,kw,kf. (82472)

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4 103 (non-embrac\* or nonembrac\*).tw,kw,kf. (0)  
5 104 (un-embrac\* or unembrac\*).tw,kw,kf. (1)  
6 105 (embrace\* or embracing).tw,kw,kf. (7691)  
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8 106 (un-accept\* or unaccept\*).tw,kw,kf. (14546)  
9 107 (unadher\* or un-adher\*).tw,kw,kf. (14)  
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11 108 no-show\*.tw,kw,kf. (484)  
12 109 (follow\* adj1 up).tw,kw,kf. (638770)  
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14 110 incent\*.tw,kw,kf. (17823)  
15 111 enabl\*.tw,kw,kf. (214935)  
16 112 disincent\*.tw,kw,kf. (859)  
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18 113 utiliz\*.tw,kw,kf. (319558)  
19 114 (inclin\* or disinclin\*).tw,kw,kf. (12034)  
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21 115 or/72-114 (2984236)  
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24 Study type / characteristics  
25 116 randomized controlled trial.pt. (387105)  
26 117 exp Randomized controlled trial/ (387132)  
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28 118 exp Randomized Controlled Trials as Topic/ (97414)  
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30 119 clinical trial.pt. (490674)  
31 120 Double-Blind Method/ (128228)  
32 121 Placebos/ (32662)  
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34 122 clinical trials as topic/ (171490)  
35 123 evaluation research/ (119973)  
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37 124 program evaluation/ (47548)  
38 125 Feasibility Studies/ (45412)  
39 126 Pilot Projects/ (85700)  
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41 127 Evaluation Studies as Topic/ (119973)  
42 128 Cost-Benefit Analysis/ (61646)  
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44 129 (random\* or non-random\* or unrandom\* or nonrandom\*).mp,kw,kf. (874470)  
45 130 placebo\*.mp,kw,kf. (168179)  
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47 131 rct\*1.tw,kw,kf. (17367)  
48 132 ((singl\* or doubl\* or trebl\* or tripl\*) adj1 (mask\* or blind\* or dumm\*)).mp,kw,kf. (176744)  
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50 133 evaluat\*.mp,kw,kf. (2416275)  
51 134 effectiv\*.mp,kw,kf. (1149619)  
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53 135 sustainab\*.mp,kw,kf. (23041)  
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56 137 appropriateness.mp,kw,kf. (12458)  
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3 138 efficac\*.mp,kw,kf. (507876)  
4 139 impact\*.mp,kw,kf. (537916)  
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6 140 (pilot adj2 (project\* or study or studies)).mp,kw,kf. (103303)  
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8 141 cost-effectiv\*.mp,kw,kf. (73309)  
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10 142 (cost\*1 adj2 benefit\*1).mp,kw,kf. (69472)  
11 143 (interrupt\* adj2 time).mp,kw,kf. (1224)  
12 144 or/116-143 (4705604)  
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14 Lower middle income countries

- 15 145 Developing Countries/ (63034)  
16 146 (Imic or Imics or lami countr\*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)  
17 147 ((developing or less\* developed or under developed or underdeveloped or middle income  
18 or low\* income or underserved or under served or deprived or poor\*) adj (countr\* or nation? or  
19 population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)  
20 148 (Afghan\* or Albania\* or Algeria\* or Angola\* or Antigua\* or Barbud\* or Argentin\* or  
21 Armenia\* or Aruba\* or Azerbaijan\* or Bahrain\* or Bangladesh\* or Barbad\* or Benin\* or Byelarus\*  
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8 or Thailand or thai or Togo or Togolese Republic or Tonga\* or Trinidad\* or Tobag\* or Tunisia\* or  
9 Turkey or turkish or Turkmenistan\* or Turkmen\* or Uganda\* or Ukrain\* or Urugua\* or USSR or  
10 Soviet Union or Union of Soviet Socialist Republics or Uzbek\* or Vanuat\* or New Hebrides or  
11 Venezuela\* or Vietnam\* or Viet Nam\* or West Bank or Yemen\* or Yugoslavia\* or Zambia\* or  
12 Zimbabw\* or Rhodesia\* or cabo verd\*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)  
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18 149 or/145-148 (4677916)  
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21 Full topic

22 150 49 and 71 and 115 and 144 and 149 (3309)

23 151 exp animals/ not (exp animals/ and exp humans/) (4003250)

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# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page # |
|------------------------------------|----|---|--------------------|
| <b>TITLE</b>                       |    |   |                    |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | 1                  |
| <b>ABSTRACT</b>                    |    |   |                    |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4                |
| <b>INTRODUCTION</b>                |    |   |                    |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | 5-6                |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 6                  |
| <b>METHODS</b>                     |    |   |                    |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | 7                  |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 7                  |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 8                  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | 8                  |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 8-9                |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 8-9                |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | 9                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 10                 |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | 10                 |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.   | 10                 |



# PRISMA 2009 Checklist

Page 1 of 2

| Section/topic                 | #  | Checklist item   | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | 10                 |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | N/A                |
| <b>RESULTS</b>                |    |  |                    |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Figure 1           |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | 11-12<br>Table 1   |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 12-13<br>Table 2   |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 14-20<br>Table 3   |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 13<br>Figure 2     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 10                 |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | N/A                |
| <b>DISCUSSION</b>             |    |  |                    |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | 20-23              |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 4, 23              |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 24                 |
| <b>FUNDING</b>                |    |  |                    |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | 25                 |



# PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

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# BMJ Open

## 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-024907.R1   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 28-Nov-2018  |
| Complete List of Authors:       | Puchalski Ritchie, LM; University of Toronto, Department of Medicine, Division of Emergency Medicine; Li Ka Shing Knowledge Institute, St. Michael's Hospital, Knowledge Translation Program<br>van Lettow, Monique; Dignitas International; University of Toronto Dalla Lana School of Public Health<br>Pham, Ba; Li Ka Shing Knowledge Institute, St. Michael's Hospital<br>Straus, Sharon; St. Michael's Hospital, Li Ka Shing Knowledge Institute; University of Toronto, Department of Medicine<br>Hosseinipour, Mina C.; University of North Carolina, Division of Infectious Disease; University of North Carolina Project<br>Rosenberg, Nora; University of North Carolina; University of North Carolina Project<br>Phiri, Sam; University of North Carolina, Department of Health Behavior, School of Public Health; Lighthouse Trust<br>Landes, Megan; University Health Network, Department of Emergency Medicine; University of Toronto, Department of Family and Community Medicine<br>Cataldo, Fabian; Dignitas International; University of Toronto, Dalla Lana School of Public Health |
| <b>Primary Subject Heading</b>: | HIV/AIDS   |
| Secondary Subject Heading:      | HIV/AIDS   |
| Keywords:                       | HIV, prevention of mother to child transmission, interventions, uptake, retention  |
|                                 |  |

SCHOLARONE™  
Manuscripts

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4 1     **What interventions are effective in improving uptake and retention of HIV-positive**  
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6 2     **pregnant and breastfeeding women and their infants in prevention of mother to child**  
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8 3     **transmission care programs in low- and middle- income countries? A systematic review**  
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10 4                                     **and meta-analysis**

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15 6     Lisa M. Puchalski Ritchie<sup>1,2,3</sup>, Monique van Lettow<sup>4,5</sup>, Ba Pham<sup>2</sup>, Sharon E. Straus<sup>1,2</sup>, Mina C.  
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17 7     Hosseinipour<sup>6,7</sup>, Nora E. Rosenberg<sup>6,7,8</sup>, Sam Phiri <sup>6,9,10,11</sup>, Megan Landes<sup>3,4,12</sup>, Fabian Cataldo<sup>4,5</sup>;  
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19 8                                     For the PURE consortium

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33 36 **Word Count: (4098)**  
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## Abstract

### Objective:

This review was conducted to identify interventions effective in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services in LMICs in order to inform program planning.

### Methods:

We conducted a systematic review of studies comparing usual care to any intervention to improve uptake and retention of HIV-positive pregnant or breastfeeding women and their children from birth to 2 years of age in PMTCT services in LMICs. Twenty-two electronic databases were searched from inception to January 15, 2018, for randomized, quazi-randomized, and non-randomized controlled trials, and interrupted time series studies; reference lists of included articles were searched for relevant articles. Risk of bias was assessed using the Cochrane Effective Practice and Organisation of Care Group criteria. Random effects meta-analysis was conducted for studies reporting similar interventions and outcomes.

### Results:

We identified 29,837 articles of which 18 studies were included in our review. Because of heterogeneity in interventions and outcome measures, only 1 meta-analysis of 2 studies and 1 outcome was conducted; we found a statistically significant increase in ART use during pregnancy for integration of HIV and antenatal care relative to standard non-integrated care (pooled AOR=2.69; 95% CI 1.25-5.78, P=0.0113). The remaining studies assessing other individual, provider, or health system interventions were synthesized narratively with small effects seen across intervention categories for both maternal and infant PMTCT outcomes based predominately on evidence with moderate to high risk of bias.



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2  
3 **69 Conclusions:**  
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6 70 The evidence on effectiveness of interventions to improve uptake and retention of mothers and  
7  
8 71 infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal  
9  
10 72 care may improve ART use during pregnancy. Future studies to replicate promising approaches  
11  
12 73 are needed. Improved reporting of key methodological criteria will facilitate interpretation of  
13  
14 74 findings and improve the utility of evidence to PMTCT program planners.  
15

16  
17 75 **Systematic review registration:** PROSPERO-CRD42015020829  
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19 76 **Key Words:** HIV, prevention of mother to child transmission, interventions, retention, uptake  
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80 **Strengths and Limitations of this review:**

- 81 • A comprehensive search was conducted, including grey literature sources and hand  
82 searching.
- 83 • A broad range of intervention categories, as well as, both maternal and infant outcomes  
84 from across the spectrum of the PMTCT cascade were included.
- 85 • Our search was limited to studies conducted in low- and middle-income countries in  
86 order to increase utility of findings to LMIC PMTCT programmers
- 87 • The multifaceted nature of the interventions and variability in outcomes reported, limited  
88 our ability to combine studies statistically.
- 89 • Due to the small number of studies included in the meta-analysis publication bias could  
90 not be examined.

91

## 92 **Introduction:**

93 In 2015, 150,000 new HIV infections and 110,000 HIV-related deaths occurred globally among  
94 children <15 years of age, with mother to child transmission the leading cause of new HIV  
95 infections among children (1,2). Despite effectiveness of prevention of mother to child  
96 transmission (PMTCT) of HIV regimens (3,4), uptake of and retention in PMTCT care remains  
97 below target in many low and middle-income countries (LMICs) (4,5,6). While progress has  
98 been made in understanding barriers to uptake and retention of women and their infants in  
99 PMTCT services (7), evidence to provide guidance to LMIC implementers and policy makers  
100 seeking to optimize PMTCT services remains limited.

101  
102 Eight systematic reviews have been conducted on strategies to optimize PMTCT. Two of these  
103 reviews evaluated the effectiveness of interventions, specifically, male involvement (8) and  
104 integration of services (9), to improve coverage of PMTCT services. These reviews were limited  
105 by the lack of studies to provide recommendations. A third review (10) examined the effects of  
106 integration of antenatal care with postnatal and other health services for a broad range of  
107 maternal health outcomes in LMICs; although some PMTCT studies and outcomes were  
108 included, this was not the focus of the review. A fourth -systematic review evaluated  
109 interventions for improving initiation of antiretroviral therapy (ART) therapy in pregnant women  
110 (11) and found the evidence quality insufficient to support recommendations. A fifth systematic  
111 review (12) assessed the impact of China's PMTCT cascade in improving uptake and outcomes  
112 at various steps along the cascade; specific interventions implemented to operationalize the  
113 cascade were not reported. Three systematic reviews have been published since the initiation of  
114 the present review. One review evaluated non-pharmacological interventions to improve quality

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3 115 of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of  
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5 116 included studies reported PMTCT outcomes, this was not a primary focus of the review. A  
6  
7 117 second review focused on postpartum retention of women in PMTCT and ART care (14). This  
8  
9 118 review focused on a limited portion of the PMTCT cascade. A third review (15) focused on  
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11 119 interventions to improve PMTCT service delivery and promote retention. This review included a  
12  
13 120 range of study designs and studies conducted in both high and low-middle income countries and  
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15 121 as such, is of less value as a guide to decision making for PMTCT policy and programming in  
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17 122 LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by:  
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19 123 lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade  
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21 124 and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high  
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23 125 income country studies where the context of PMTCT care is often substantially different than in  
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25 126 LMICs.  
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33 128 This review was developed in collaboration with knowledge users from the Malawi Ministry of  
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35 129 Health's HIV treatment and care technical working group. The objective of this current review  
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37 130 was to identify what interventions at the patient, provider, or health system level are effective  
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39 131 compared to no intervention or usual care in improving uptake and retention of HIV-positive  
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41 132 mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health  
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43 133 services in LMICs, this review is targeted to provide guidance for PMTCT policy and  
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45 134 programming in LMICs, and therefore included a broad range of intervention categories, as well  
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47 135 as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.  
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**Methods:**

*Protocol:* A protocol was developed for this review based on the Cochrane Handbook for systematic reviews (16) and the Cochrane Effective Practice and Organisation of Care Group (EPOC) (17) and registered with PROSPERO (CRD42015020829, available at: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015020829#VXHCNUZBn5I](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020829#VXHCNUZBn5I)). The complete protocol was previously published and the methods are presented briefly here (18). Our findings are reported using the PRISMA statement for reporting systematic reviews (19).

*Patient and Public Involvement:*

No patients were involved in this study.

*Eligibility Criteria:*

We included studies reporting the effectiveness of interventions in improving uptake and/or retention of HIV-positive pregnant or breast feeding women and their children from birth to 2 years of age or termination of breast feeding in PMTCT services. We included randomized, quasi-randomized and non-randomized controlled trials, and interrupted time series studies that compared usual care or no intervention to any type of intervention at the patient, provider, or health system level. Although included in error in the Prospero registration for our review, controlled before and after studies were not included in the protocol manuscript or search. Studies were included if conducted in LMICs as defined by the EPOC filter (20) and updated using the most recent World Bank World Country and Lending group classification (21). Studies that included both high and low/middle- income countries were eligible for inclusion if LMICs

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3 161 results could be abstracted. No restriction was placed based on language of publication,  
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5 162 publication status, study time frame, or duration of follow-up.  
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10 164 Information Sources and Literature Search:  
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12 165 A search strategy was developed in consultation with an experienced information specialist  
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14 166 (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review  
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16 167 of Electronic Search Strategies checklist (22). The following databases were searched from  
17  
18 168 inception to July 31, 2015 and subsequently updated using the same search strategy for the  
19  
20 169 period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV,  
21  
22 170 pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and  
23  
24 171 retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global  
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26 172 Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science,  
27  
28 173 Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE,  
29  
30 174 ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library,  
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32 175 WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov.  
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34 176 Several databases planned for inclusion in our search were no longer available or not accessible  
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36 177 by our group at the time of the search and were therefore not included: AIDS Education Global  
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38 178 Information System, British Library Catalogue, and the New York Academy of Grey Literature.  
39  
40 179 In addition, we searched reference lists of included articles, and contacted several experts in the  
41  
42 180 field to inquire about eligible unpublished or in progress studies. See supplementary file for  
43  
44 181 complete MEDLINE search strategy.  
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54 183 Study Selection and Data Collection Process:  
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3 184 A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a  
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5 185 sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement.  
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7 186 Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then  
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9 187 abstracts were screened, and second, the full-text articles were screened. Translation software  
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11 188 was utilized to screen articles at the titles and abstracts level, with no non-English articles  
12  
13 189 remaining at the full article review phase. A data abstraction form was created using the EPOC  
14  
15 190 data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in  
16  
17 191 screening and data extraction. A calibration exercise was conducted with completed data  
18  
19 192 extraction forms compared and discussed for each of the first 3 articles to ensure consistency;  
20  
21 193 data extraction was then completed for the remaining articles independently and in duplicate by 2  
22  
23 194 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each  
24  
25 195 study included: population, intervention, comparator, context, outcomes, study design, time  
26  
27 196 frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes  
28  
29 197 were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment,  
30  
31 198 percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis,  
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33 199 and percentage of women and infants retained in PMTCT care/completing the ART regimen as  
34  
35 200 defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of  
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37 201 infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants  
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39 202 completing post-exposure HIV testing 6 weeks following termination of breast feeding for all  
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41 203 infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV;  
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43 204 adverse events; major or minor congenital malformations; small for gestational age; pre-mature  
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45 205 delivery; still birth; and infant death within first 2 years of life (18).  
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3 207 When necessary to clarify published data or to obtain unpublished data, we contacted primary  
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5 208 authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions,  
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8 209 and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to  
9  
10 210 calculate risk ratios were not available in the publication. Three responded and provided the  
11  
12 211 requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional  
13  
14 212 data as they were submitting the manuscript for publication.  
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19 214 Methodological Quality/Risk of Bias Appraisal:

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21 215 Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the  
22  
23 216 Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies  
24  
25 217 included in the meta-analysis, risk of publication bias could not be examined using funnel plots.  
26  
27 218 Selective reporting bias was assessed through review of trial registrations where available and  
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29 219 categorized as unclear if not registered.  
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35 221 Data Synthesis:

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37 222 Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy  
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39 223 for health system interventions and discrepancies resolved through discussion (23). Clinical  
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41 224 heterogeneity was determined based on patient, intervention, and outcome characteristics.  
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43 225 Descriptive synthesis of study results were conducted for all studies, and are reported narratively  
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45 226 and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate  
46  
47 227 intervention effects using the Metafor Package in the statistical software R (24). Statistical  
48  
49 228 heterogeneity was examined using the  $I^2$  statistic, with  $I^2 \geq 75\%$  indicating significant  
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51 229 heterogeneity (16).  
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231 **Results:**232 Literature Search:

233 A total of 29,837 articles were identified through the database and hand search. After duplicates  
 234 were removed 21,354 titles and abstracts were screened and 95 articles reviewed in full. Thirty-  
 235 four articles representing 18 studies with 16 companion reports met eligibility criteria (Figure 1,  
 236 flow diagram).

237

238 Study Characteristics:

239 Study characteristics are outlined in Table 1 (see supplementary file table for complete study  
 240 characteristics).

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242 Table 1: Characteristics of Included Studies

| Author(s); Year | Intervention Level/Type | Study Design                              | Country; Geographic Location in Country           | Study Population  | Intervention   | Comparison | Intervention Classification EPOC            | Number of Participants     | Participant Characteristics   | Outcomes   |
|-----------------|-------------------------|---|---|---|--|------------|---|----------------------------|---|--|
| Ezeanolue; 2015 | Patient                 | Mixed Methods Including Small Cluster RCT | Nigeria (Enugu state)                             | Self-identified pregnant women $\geq 18$ years who attended any church site | Monthly baby showers offered health education and onsite laboratory testing including HIV testing, and Mama Packs for essential items during pregnancy | Usual care | • Outreach services                         | 40 churches, 3002 patients | • % HIV positive: 2% overall<br>• Maternal age (mean): I = 29.3, C = 29.7 | 1) ART during pregnancy<br>2) Retention in care at 6-8 week postpartum |
| Reynolds; 2010  | Patient                 | Cluster RCT                               | Kenya (Coast, Rift Valley, and Western provinces) | HIV-positive pregnant women $\geq 18$ and at least 32 weeks gestation       | PMTCT providers trained to prepare and counsel women on how to store and   | Usual care | • Self-management<br>• Educational outreach | 10 Clusters: 160 patients  | • Maternal age (mean): I = 27.4, C = 28.4                                 | Infant ART prophylaxis at birth  |



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|----------------|------------------|-------------|--|--|--|--|--|-----------------------------|--|--|
|                |                  |             |  |  | administer take-home nevirapine infant dose  |  |  |                             |  |  |
| Weiss; 2014    | Patient          | RCT         | South Africa (Gert Sibande and Nkangala districts) | HIV-positive pregnant women, 24 to 30 weeks gestation, and ≥18 years of age, recruited and asked to invite their male partner to enroll as a couple. | 4 successive weekly sessions employed a cognitive-behavioral approach and addressed HIV, safer sex, sexual negotiation, and PMTCT issues. Sessions were closed, structured, of gender-concordant groups, led by trained gender-matched facilitators, and conducted in ANCs.                          | Time-matched health education sessions | • Group (couple) vs individual care              | 12 Clusters<br>478 couples  | • % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive<br>• Maternal age (mean): I = 28.3; C = 28.1 | 1) ART detected in mother blood samples at birth<br>2) ART detected in infants blood at birth<br>3) Infant HIV-positive rate at 6 weeks            |
| Yotebing; 2016 | Patient          | RCT         | Democratic Republic of Congo (Kinshasa)            | Newly diagnosed HIV-positive women, ≤32 weeks gestation, registering for ANC   | Participants received small escalating cash payments, starting at US \$5 and increasing by \$1 each visit. If attended scheduled clinic appointments and completed recommended actions. Incentive reset to its original value if mother failed to complete any actions required at a specific visit. | Usual care                             | • Conditional cash transfer                      | 433 women                   | • Maternal age (median): I = 29.5, C = 29.0  | 1) Retention in care at 6 weeks postpartum<br>2) Uptake of PMTCT services through to 6 weeks postpartum<br>3) Infant HIV-positive rates at 6 weeks |
| Richter, 2014  | Patient/Provider | Cluster RCT | South Africa (KwaZulu-Natal)                       | HIV-positive women, ≥18 years of age and <34 weeks   | 8-session intervention conducted by peer mentors (4 antenatal,   | Usual care                             | • Role expansion or task shifting<br>• Education | 8 Clusters<br>1200 patients | • Maternal age (mean):(I = 26.5; C = 26.5  | 1) ART from the 28th week of pregnancy (AZT  |

|                       |                 |                        |                     |   |  |            |   |                             |  |  |
|-----------------------|-----------------|------------------------|---------------------|---|--|------------|---|-----------------------------|--|--|
|                       |                 |                        |                     | pregnant  | 4 postnatal) to support HIV-positive women through pregnancy and early motherhood. HIV-positive women recruited, trained and certified as peer mentors prior to implementation; in-person supervision was provided weekly.                               |            | al meetings   |                             |  | or HAART )<br>2) ART during labor (AZT or HAART<br>3) NVP or HAART during labor<br>4) Infant NVP at birth<br>5) AZT dispensed for infant and medicated as prescribed |
| Kieffer; 2011         | Provider        | Cluster RCT            | Swaziland           | All pregnant women presenting for delivery at participating maternity facilities        | 1-day training course provided to nurse-midwives to increase knowledge and skills in provision of PMTCT and to enhance confidence and counseling skills.   | Usual care | • Educational meetings  | 6 Clusters<br>2444 Patients | % HIV positive at enrollment: 33% overall  | NVP in cord blood  |
| Dryden-Petersen; 2015 | Provider/System | Step wedge Cluster RCT | Botswana (Gaborone) | ART-naïve, HIV-positive women registering at antenatal clinic before 26 weeks gestation | 2-hour clinical staff education sessions on protocols for CD4 testing; open-source platform permitting automated SMS to monitor/deliver CD4 results between central labs and clinics; longitudinal support for tracing women eligible for ART initiation | Usual care | • The use of information and communication technology<br>• Educational meetings | 19 Clusters<br>336 women    | % HIV positive: I = 189 (47.6%) and C = 177 (44.6%)<br>• Maternal age (median): (I = 28; C = 29) | ART initiation by 30 wks gestation   |

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|-----------------------|---------------------|------------------------------|---|--|---|---|---|--|---|--|
| Mwapa<br>sa;<br>2017  | Provider/Sy<br>stem | 3<br>Arm,<br>Cluste<br>r RCT | Malawi<br>(Salima<br>and<br>Mangoch<br>i<br>districts)    | HIV-<br>positive<br>pregnant<br>women<br>initiated<br>on<br>Option<br>B+<br>regimen  | MIP-<br>integration<br>of<br>HIV/ANC,<br>routine<br>tracing<br><br>MIP +<br>SMS,<br>integrated<br>HIV/ANC<br>care, SMS<br>sent to<br>community<br>health<br>worker to<br>trace if<br>appointme<br>nt missed | Usual<br>care:<br>non-<br>integrate<br>d care,<br>routine<br>tracing<br>as for<br>MIP | •<br>Integration<br>• The use<br>of<br>informatio<br>n and<br>communic<br>ation<br>technology | 30<br>Clusters<br>1350<br>women  | • Maternal<br>age<br>(median):<br>MIP = 29.5;<br>MIP+SMS<br>= 29.2;<br>SOC = 29.4 | 1)<br>Materna<br>l<br>retentio<br>n in<br>care at<br>12<br>months<br>postpart<br>um trial<br>data<br>2) Infant<br>retentio<br>n in<br>care at<br>12<br>months<br>postpart<br>um trial<br>data<br>3)<br>Materna<br>l<br>retentio<br>n in<br>care at<br>12<br>months<br>using<br>MOH<br>definitio<br>n<br>4) Infant<br>retentio<br>n in<br>care at<br>12<br>months<br>using<br>MOH<br>definitio<br>n |
| Oyeled<br>un;<br>2017 | Provider/Sy<br>stem | Cluste<br>r RCT              | Northern<br>Nigeria<br>(Benue<br>and<br>Kaduna<br>states) | HIV-<br>positive,<br>women,<br>gestation<br>al age <=<br>34<br>weeks,<br>who were<br>ART<br>naive and<br>agreed to<br>start<br>lifelong<br>ART | QI teams<br>established<br>, visits by<br>coaches<br>and<br>collaborativ<br>e meetings  | Routine<br>MOH<br>support   | •<br>Continuou<br>s quality<br>improvem<br>ent  | 32<br>Clusters:<br>(6 later<br>excluded<br>)<br>532<br>women<br>(21<br>withdrew<br>leaving<br>511 in<br>total) | • Maternal<br>age<br>(median): I<br>= 27 ; C =<br>27                              | 1) ART<br>initiated<br>within 2<br>week of<br>enrolme<br>nt<br>2)<br>Retenti<br>on in<br>care at<br>6<br>months<br>3)<br>Infants<br>starting<br>prophyl<br>axis<br>within<br>72<br>hours<br>4) infant<br>HIV<br>testing<br>at 6-10<br>weeks  |
| Phiri;<br>2017        | Provider/Sy<br>stem | 3<br>Arm,<br>Cluste<br>r RCT | Malawi<br>(SE, SW<br>and<br>Central<br>West               | Pregnant<br>and<br>breastfee   | FBPS -<br>women<br>received<br>SOC and<br>met with  | SOC =<br>standard<br>of care<br>facilities<br>provided                                | • Role<br>expansion<br>or task<br>shifting<br>outreach  | 21<br>Clusters<br>1269<br>women  | • Maternal<br>age<br>(median<br>across all 3                                      | 1) ART<br>uptake<br>2)<br>Retaine<br>d in  |

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|  |  | Zones) | ding HIV-positive women and their infants. Up to 3 male sex partners could be enrolled per patient. | “mentor mothers”, HIV-positive women who had recently completed PMTCT and were on ART. Mentor mothers provided 1-on-1 support at each clinic visit, led weekly clinic-based support groups, and contacted women within 1 week of a missed appointment.<br><br>CBPS-women received SOC and met with “expert mothers”, HIV-positive women who recently completed PMTCT and were on ART. Expert mothers conducted routine home visits to provide HIV education and clinic visit reminders, and led monthly community-based support group meetings. Expert mothers were responsible for contacting women in the community | routine HIV care according to Malawi MOH guidelines. According to national guidelines, women who fail to attend the clinic within 60 days of a missed appointment are supposed to be traced. However, this rarely occurs in the routine program. | services<br>• The use of information and communication technology |  | arms): 27 | care at 1 year:<br>3) Retained in care at 2 years trial data<br>4) Retained in care at 2 years MOH definition<br>5) Infant HIV tested at 6 weeks<br>6) Infant HIV-positive at 6 weeks |
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|                        |                     |                 |   |  | within 1 week of a missed clinic visit.  |   |  |                                   |  |   |
| Tomlins<br>on;<br>2014 | Provider/Sy<br>stem | Cluste<br>r RCT | South<br>Africa<br>(Umlazi)                               | Pregnant<br>women<br>aged ≥17<br>and their<br>newborns<br>residing<br>in the<br>clusters<br>during<br>the<br>recruitme<br>nt period  | CHWs<br>were<br>trained to<br>carry out<br>structured<br>home visits<br>using<br>motivationa<br>l<br>interviewin<br>g for<br>breastfeedi<br>ng<br>counseling.<br>Women<br>were<br>scheduled<br>to receive<br>7 home-<br>based<br>visits<br>during<br>pregnancy<br>and post-<br>delivery.<br>Low birth<br>weight<br>neonates<br>received 2<br>extra visits<br>within the<br>first week  | In control<br>clusters,<br>CHWs<br>provided<br>informati<br>on and<br>support<br>on<br>accessin<br>g social<br>welfare<br>grants<br>and<br>conducte<br>d three<br>home-<br>based<br>visits:<br>during<br>pregnanc<br>y and<br>post-<br>delivery.                | • Role<br>expansion<br>or task<br>shifting<br>• Outreach<br>services             | 30<br>Clusters<br>3957<br>women   | Maternal<br>age<br>(median): I<br>= 23; C =<br>23    | 1) Infant<br>HIV<br>testing<br>by 6<br>weeks<br>2)<br>Infant<br>HIV-<br>positive<br>at 12<br>weeks  |
| Aliyu;<br>2016         | System              | Cluste<br>r RCT | Rural<br>north-<br>central<br>Nigeria<br>(Niger<br>State) | HIV-<br>positive<br>women<br>and their<br>infants,<br>presentin<br>g for ANC<br>or<br>delivery<br>who met<br>1 of<br>following<br>criteria:<br>unknown<br>HIV<br>status at<br>presentati<br>on;<br>history of<br>ART<br>prophylax<br>is or<br>treatment<br>, but not<br>receiving<br>ARTs at<br>presentati<br>on; or<br>known<br>HIV<br>status but<br>had never<br>received<br>treatment | Integrated<br>package of<br>PMTCT<br>services<br>that<br>included<br>point-of-<br>care CD4<br>cell count<br>or<br>percentage<br>testing,<br>transition<br>of<br>decentraliz<br>ed PMTCT<br>tasks to<br>trained<br>midwives,<br>integrated<br>mother and<br>infant care<br>services,<br>active<br>influential<br>family<br>member<br>(male<br>partner)<br>participatio<br>n, and<br>community<br>involvemen<br>t (male<br>community<br>peer<br>champions<br>providing | Standard<br>of care<br>included<br>health<br>informati<br>on, opt-<br>out HIV<br>testing,<br>infant<br>feeding<br>counselin<br>g,<br>referral<br>for CD4<br>cell<br>counts<br>and<br>treatment<br>, ART<br>prophyla<br>xis, and<br>early<br>infant<br>diagnosis | • Role<br>expansion/<br>task<br>shifting<br>Integration<br>• Packages<br>of care | 12<br>Clusters<br>369<br>patients | • Maternal<br>age<br>(median): I<br>= 26 ; C =<br>28 | 1)<br>Materna<br>l ART<br>initiation<br>2)<br>Materna<br>l-infant<br>retentio<br>n in<br>care at<br>6 week<br>postpart<br>um<br>3)<br>Materna<br>l-infant<br>retentio<br>n in<br>care at<br>12<br>weeks<br>post<br>partum |

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|-----------------------|--------|------------------------|----------------------------|---|---|------------|--|---|--|--|
|                       |        |                        |                            |   | outreach, education, and linkage of male partners to key referral services)   |            |  |   |  |  |
| Geelhoed; 2013        | System | Cluster RCT            | Mozambique (Tete province) | Public primary health facilities providing maternal child health and PMTCT services Mothers and their children up to 5 years of age.                      | Reorganized services to deliver integrated consultations and services for mothers and their children up to 5 years of age.  | Usual care | <ul style="list-style-type: none"> <li>Integration</li> <li>Educational meetings</li> </ul>                  | 6 Clusters  | Not available  | 1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 3) Infant HIV-positive |
| Killam; 2010          | System | Step wedge Cluster RCT | Zambia (Lusaka)            | ART eligible pregnant women presenting at participating clinics   | Integration of ART care into ANC. Women already receiving ART at the general ART clinic encouraged to continue receiving their services in the general ART clinic     | Usual care | <ul style="list-style-type: none"> <li>Integration</li> </ul>  | 8 Clusters 31536 patients                           | <ul style="list-style-type: none"> <li>% HIV positive: I = 21.8%; C = 22.2%</li> <li>Maternal age (mean): I = 27.5; C = 27.3</li> </ul>  | ART initiation during pregnancy  |
| Odeny; 2014           | System | RCT                    | Kenya (Nyanza region)      | HIV-positive women attending antenatal or HIV care; >=18 years of age; between 28 weeks gestation and delivery; enrolled in PMTCT; access to mobile phone | Custom-built, automated software to send and receive text messages. Sent 14 text messages, up to 8 sent during pregnancy, and weekly for first 6 weeks after delivery | Usual care | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul>        | 388 Patients  | <ul style="list-style-type: none"> <li>% HIV positive: 29.3% (388/1324)</li> <li>Maternal age (mean): (I = 30.8% 18-24, 56.9% 25-34, 12.3% 35+; C = 33.7% 18-24, 57.5% 25-34, 8.8% 35+)</li> </ul> | 1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks     |
| Rotherham-Borus; 2014 | System | Cluster RCT            | South Africa (Cape Town)   | Pregnant women >= 18 years of age from Cape Town townships  | Antenatal and postnatal home visits by CHW in addition to standard clinic-based care  | Usual care | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Outreach services</li> </ul> | 26 Clusters: (2 later removed); 1144 eligible women | <ul style="list-style-type: none"> <li>%HIV positive: I = 149 (25.5%); C = 146 (26.7%)</li> <li>Mean maternal age: I = 26.5; C = 26.3</li> </ul>   | 1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART                       |

|               |        |             |                                  |   |   |   |                                  |                              |  |  |
|---------------|--------|-------------|----------------------------------|---|---|---|----------------------------------|------------------------------|--|--|
|               |        |             |                                  |   |   |   |                                  |                              |  | at onset of labor<br>4) Infant prophylaxis within 24 hours of birth<br>5) AZT dispensed for infant and medicated as prescribed<br>6) Infant HIV test at 6 weeks  |
| Rustagi; 2016 | System | Cluster RCT | Cote d'Ivoire, Kenya, Mozambique | Public and non-profit health facilities with PMTCT services. Pregnant women presenting for antenatal care | A five-step, facility-level systems analysis and improvement intervention designed to maximize effectiveness of PMTCT service delivery by improving understanding of inefficiencies   | Usual care  | • Continuous quality improvement | 36 Clusters<br>1876 patients | Not available  | 1) ART in pregnancy<br>2) Infants HIV tested by 6-8 weeks  |
| Turan; 2015   | System | Cluster RCT | Kenya (Nyanza Province)          | Pregnant HIV-positive women >= 18, not enrolled in HIV care at baseline and their infants                 | Integrated clinics provided PMTCT and HIV care and treatment services within existing ANC services, starting prenatally and continuing until a definitive pediatric HIV diagnosis was obtained or the child reached 18 months of age. | Non-integrated ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women to a separate HIV clinic at the same facility | • Integration                    | 12 Clusters:<br>1172 women   | • %HIV positive: I = 48.5%, C = 51.5%<br>• Maternal age (mean): I = 25.0, C = 24.8 | 1) ART during pregnancy<br>2) ART during Labor<br>3) ART after birth<br>4) Infant ART after birth<br>5) ART use throughout all 3 PMTCT periods<br>6) Infant HIV testing by 3 months<br>7) Infant HIV testing at 9 months |

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|  |  |  |  |  |  |  |  |  |  | 8)<br>Infants<br>HIV<br>tested<br>by 6<br>weeks<br>9)<br>Infants<br>HIV-<br>positive<br>at 6<br>weeks<br>10)<br>Infants<br>HIV<br>tested<br>by end<br>of study<br>(up to<br>12<br>months)<br>11)<br>Infants<br>HIV-<br>positive<br>at 9<br>months |
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245 The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge  
 246 design, and 2 RCTs. The number of clusters ranged from 6 to 40, and participants across all  
 247 study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan  
 248 Africa between 2005 and 2016. Half of included studies reported multifaceted interventions  
 249 including 2 or more EPOC category components [9/18] and as a result several were categorized  
 250 at more than 1 intervention level: patient [4], provider [1], system [7], patient/provider [1], or  
 251 provider/system [5]. Interventions directed all or in part to the health system level were most  
 252 common [12/18]. Integration [5/18], role expansion or task shifting [5/18], outreach services  
 253 [4/18], and use of information and communication technology [4/18] were the most common  
 254 EPOC intervention categories employed alone or as part of a complex intervention.

255

256 Reporting of population characteristics varied widely across studies as did outcome definitions.

257 Seven studies limited participation to pregnant women 17-18 years of age or older; median ages



1  
2  
3 258 across the studies ranged from 23 to 29.7 years. Marital status was reported in 14 studies, and  
4  
5 259 varied widely from 9% to 99% of women who were married or had a live-in partner. Maternal  
6  
7 260 education level was reported in 12 studies; 5 studies reported the majority of women having no  
8  
9 261 or primary education, 5 studies reported the majority of women having received secondary  
10  
11 262 education, and, 2 reported mean/median years of education [10.3 years, 10 years [range 8-  
12  
13 263 12years]]. Maternal employment [6/18] and parity [2/18] status were reported in a minority of  
14  
15 264 studies (Table 1). No pre-specified adverse events were reported in the identified studies.  
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22 266 Reported outcomes varied substantially across studies, with few studies within intervention  
23  
24 267 categories reporting comparable outcomes. For example, 5 studies reported interventions  
25  
26 268 employing integration alone [2] or in combination with other interventions [3], with only 1  
27  
28 269 PMTCT outcome in common among the 2 studies employing integration alone. The most  
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30 270 commonly reported outcomes were maternal ART use during pregnancy and labor and delivery,  
31  
32 271 infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.  
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38 273 As a result of the multifaceted nature of the majority of interventions employed, and variability  
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40 274 in PMTCT outcomes reported, the ability to combine results statistically was limited.  
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#### 44 276 Methodological Quality:

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47 277 Risk of bias was assessed using the Cochrane EPOC risk of bias criteria (17). Five of the 18  
48  
49 278 studies were appraised as low risk of bias on 3 or more (4 with 3, 1 with 4) of the 6 main criteria.  
50  
51 279 The most common issues encountered were unclear reporting of randomization (8/18) and  
52  
53 280 allocation concealment (11/18), and unclear reporting or high risk of bias due to lack of blinding  
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281 of participants/personnel (18/18) and blinding of outcome assessment (16/18) (The complete risk  
282 of bias table is included as an additional file).

283  
284 Meta-analysis of Effect of Integration of care on ART use during pregnancy:

285 We expected variation in the implementation of integrated care of ART therapy into ANC in the  
286 two studies, conducted in clinics in Zambia and Kenya. We also expected some variation in  
287 standard care in the two settings, particularly with respect to eligibility and timing of ART  
288 initiation across the two studies both of which experienced policy changes during the course of  
289 the study. We therefore used a random-effects meta-analysis to derive the combined effect  
290 estimate of integrated care based on theoretical grounds although the  $I^2$  was not significant.

291 Two studies assessing integration of HIV and antenatal care relative to usual non-integrated care  
292 were combined in a meta-analysis of 1,887 patients (25,26); there was increased use of ARTs  
293 during pregnancy with integration of HIV and antenatal care compared to standard non-  
294 integrated care, non-integrated care, (AOR=2.69; 95% CI=1.25, 5.78; P=0.0113,  $I^2=59.26\%$ )  
295 (Figure 2) (see supplementary file for fixed effects meta-analysis diagram) .

296  
297 Descriptive Synthesis:

298 Details of included studies (country, intervention, population characteristics, outcomes, etc.) and  
299 outcomes are outlined in Table 1 and 2.

300  
301 Table 2: Results of Included Studies

| Author: Year    | Intervention Level/Type | Intervention Classification EPOC | Intervention         | Control    | Outcomes Intervention Group          | Outcomes Control Group               | Risk Ratio (95%CI)    | Adjusted Statistic where provided |
|-----------------|-------------------------|----------------------------------|----------------------|------------|--------------------------------------|--------------------------------------|-----------------------|-----------------------------------|
| Ezeanolue; 2015 | Patient                 | • Outreach                       | Monthly baby showers | Usual care | 1) ART during pregnancy: 24/41 (65%) | 1) ART during pregnancy: 12/32 (50%) | 1) 1.56 (0.93 - 2.62) | 1) AOR 2.8 (1.02-4.79)            |

|                         |                  |   |   |   |  |   |   |  |
|-------------------------|------------------|---|---|---|--|---|---|--|
|                         |                  | services  |   |   | 2) Retention in care at 6-8 week postpartum: 33/41(81%)  | 2) Retention in care at 6-8 week postpartum: 28/32(88%)   | 2) 0.92 (0.75-1.12)   | 2) AOR 0.39 (0.04-3.99)  |
| Reynolds; 2010          | Patient          | <ul style="list-style-type: none"> <li>Self-management</li> <li>Educational outreach</li> </ul>                 | Take home infant nevirapine dose  | Usual care                              | Infant ART prophylaxis at birth: 80/85 (94%)   | Infant ART prophylaxis at birth: 66/75 (88%)  | 1.07 (0.97-1.18)  | --   |
| Weiss; 2014             | Patient          | <ul style="list-style-type: none"> <li>Group (couple) vs. individual care</li> </ul>                            | Couples HIV risk reduction and PMTCT education sessions                         | Time matched general education sessions | 1) ART detected in mother blood samples at birth: 9/12 (75%)<br>2) ART detected in infants blood at birth: 12/13 (92%)<br>3) Infant HIV positive at 6 weeks: 1/30 (3.3%)   | 1) ART detected in mother blood samples at birth: 16/12 (50%)<br>2) ART detected in infants blood at birth: 9/12 (75%)<br>3) Infant HIV positive: 3/39 (7.7%)   | 1) 1.50 (0.78-2.88)<br>2) 1.23 (0.86-1.77)<br>3) 0.43 (0.05-3.96)   | --   |
| Yotebieng; 2016         | Patient          | <ul style="list-style-type: none"> <li>Conditional cash transfer</li> </ul>                                     | Cash payments for clinic attendance and acceptance of recommended services      | Usual Care                              | 1) Retention in care at 6 weeks postpartum: 174/216 (80.6%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 146/216 (67.6%)<br>3) HIV positive infants at 6 weeks: 5/169 (3.0%)  | 1) Retention in care at 6 weeks postpartum: 157/217 (72.4%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%)<br>3) HIV positive infants at 6 weeks: 6/156 (3.9%)   | 1) 1.11(1.00-1.23)<br>2) 1.26(1.08-1.48)<br>3) 0.77(0.24-2.47)  | 1) ARD 1.13 (1.02-1.26)<br>2) ARD 1.31 (1.12-1.54)<br>3) –   |
| Richter, 2014           | Patient/Provider | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Educational meetings</li> </ul> | Peer Mentor led educational meetings  | Usual Care                              | 1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%)<br>2) ART during labor (AZT or HAART): 282/377 (74.8%);<br>3) NVP or HAART during labor: 361/377 (95.8%)<br>4) Infant NVP at birth: 364/377 (96.6%)<br>5) AZT dispensed for infant and medicated as prescribed: 348/377 (92.3%) | 1) ART from the 28th week of pregnancy (AZT or HAART): 455/466 (95.5%)<br>2) ART during labor (AZT or HAART): 334/466 (71.7%)<br>3) NVP or HAART during labor: 456/466 (97.9%)<br>4) Infant NVP at birth: 451/466 (96.8%)<br>5) AZT dispensed for infant and medicated as prescribed: 374/466 | 1) 0.92 (0.89-0.96)<br>2) 1.04 (0.96-1.13)<br>3) 0.98 (0.95-1.00)<br>4) 1.00 (0.97-1.02)<br>5) 1.15 (1.09-1.21) | 1) AOR 0.44 (0.26,0.74)<br>2) AOR 1.16(0.44, 3.02)<br>3) AOR 0.53 (0.20, 1.41)<br>4) AOR 1.00 (0.36, 2.79)<br>5) AOR 2.98 (0.78,11.30) |
| Kieffer; 2011           | Provider         | <ul style="list-style-type: none"> <li>Educational meetings</li> </ul>  | 1 day PMTCT training for nurses and midwives                                    | No additional training                  | NVP in cord blood: 373/465(80%)  | NVP in cord blood: 325/472 (69%)  | 1.17 (1.08, 1.26)   | ---  |
| Dryden - Peterson; 2015 | Provider/System  | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul>           | Staff training in point of care CD4 testing and automated SMS results reporting | Usual care                              | ART initiated by 30 wks gestation: 56/154 (36.4%)  | ART initiated by 30 wks gestation: 37/153 (24.2%)   | 1.50 (1.06-2.13)  | AOR 1.06 (0.53,2.13)   |

|                |                  |  |  |   |  |   |   |  |
|----------------|------------------|--|--|---|--|---|---|--|
|                |                  | • Educational meetings   | to staff, support for patient tracing  |   |  |   |   |  |
| Mwapa sa; 2017 | Provider/Sy stem | • Integration of information and communication technology  | MIP= integration of antenatal and HIV care, routine patient tracing<br>MIP+SMS , integrated care and use of SMS enhanced tracing | Usual non-integrated care and patient tracing | 1) Maternal retention in care at 12 months postpartum trial data: MIP 89/461, 19.3%<br>MIP+SMS 115/493<br>2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3%<br>MIP+SMS 82/399, 20.1%<br>3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4%<br>MIP+SMS 332/493, 67%.<br>4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4%<br>MIP+SMS 323/399, 80.9% | 1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7%<br>2) Infant retention in care at 12 months postpartum trial data: SOC 32/300, 10.7<br>3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1%<br>4) Infant retention in care at 12 months using MOH definition: SOC 234/300, 78.0% | 1) MIP vs SOC 0.85 (0.65-1.10), MIP+SMS vs SOC 1.03 (0.81-1.31)<br>2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82)<br>3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06)<br>4) MIP vs SOC 0.97 (0.89-1.05), MIP+SMS vs SOC 1.04(0.96-1.12) | 1) MIP vs SOC ARR 0.85 (0.56-1.30), MIP+SMS vs SOC ARR 1.08 (0.87-1.35)<br>2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31)<br>3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05)<br>4) MIP vs SOC ARR 0.98 (0.89-1.09), MIP+SMS vs SOC ARR 1.01 (0.96-1.07) |
| Oyeledun; 2017 | Provider/Sy stem | • Continuous quality improvement   | QI teams established, coaching, and collaborative meetings   | Routine MOH support                           | 1) ART initiated within 2 week of enrolment: 233/247 = 94.3%<br>2) Retention in care at 6 months. 102/247 = 41.3%<br>3) Infants starting prophylaxis within 72 hours : 138/209 = 66%<br>4) Infant HIV testing at 6-10 weeks 102/209 = 48.8%;   | 1) ART initiated within 2 week of enrolment: 233/247 = 94.3%<br>2) Retention in care at 6 months. 102/247 = 41.3%<br>3) Infants starting prophylaxis within 72 hours 145/194 = 74.7%<br>4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%   | 1) 1.05 (1.01-1.08)<br>2) 1.07 (0.88-1.31)<br>3) 0.88 (0.78-1.00)<br>4) 1.93 (1.46-2.55)  | 1) --<br>2) ARR 1.08(0.78, 1.49)<br>3) ARR 0.95 (0.84, 1.07)<br>4) ARR 1.76(1.27, 2.42)  |
| Phiri; 2017    | Provider/Sy stem | • Role expansion or task shifting outreach services<br>• The use of information and communication technology | FBPS – facility based peer support from mentor mothers<br>CBPS- community based peer support from                                | SOC- standard of care                         | 1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%)<br>2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%)<br>3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394   | 1) ART uptake: SOC- 361/447(81%)<br>2) Retained in care at 1 year: SOC- 261/361 (74%)<br>3) Retained in care at 2 years (trial data): SOC- 169/447 (38%)  | 1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06-1.18)<br>2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10)<br>3) SOC vs FBPS 1.38(1.19-   | 1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18)<br>2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20)<br>3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30)<br>4) --  |

|                 |                 |  |  |   |  |  |   |  |
|-----------------|-----------------|--|--|---|--|--|---|--|
|                 |                 |  | mentor mothers   |   | (54%)<br>4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%)<br>5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%)<br>6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%) | 4) Retained in care at 2 years (MOH definition): SOC- 255/447(57%)<br><br>5) Infant HIV test at 6 weeks: SOC- 169/273(62%)<br><br>6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)                          | 1.60), SOC vs CBPS 1.42 (1.22-1.65)<br>4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43)<br>5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38)<br>6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09) | 5) --<br><br>6) ---  |
| Tomlinson; 2014 | Provider/System | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Outreach services</li> </ul>                     | 10 structured home visits from community health workers providing support in accessing social welfare grants | 3 home visits from community health workers | 1) Infant HIV testing by 6 weeks: 420/571(73.6%)<br>2) Infant HIV positive at 12 weeks: 28/568 (4.9%)  | 1) Infant HIV testing by 6 weeks: 465/698(66.6%)<br>2) Infant HIV positive at 12 weeks: 32/697 (4.6%)  | 1) 1.10 (1.03-1.19)<br>2) 1.07 (0.65-1.76)  | 1) ARR 1.10 (0.97, 1.25)<br>2) ARR 1.07 (0.69,1.66)                    |
| Aliyu; 2016     | System          | <ul style="list-style-type: none"> <li>• Role expansion /task shifting</li> <li>• Integration</li> <li>• Packages of care</li> </ul> | Integrated package of PMTCT services, family/male partner participation, community champions                 | Usual Care                                  | 1) Maternal ART initiation for PMTCT:166/172 (97%)<br>2) Maternal-infant retention in care at 6 weeks postpartum: 125/150 pairs (83%)<br>3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)                                   | 1) Maternal ART initiation for PMTCT: 77/197 (39%),<br>2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%)<br>3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%) | 1) 2.47 (2.07-2.95)<br>2) 9.44 (5.60-15.40)<br>3) 11.40 (6.40-20.34)  | 1) ARR 3.3 (1.4-7.8)<br>2) ARR 9.1 (5.2-15.9)<br>3) ARR 10.3(5.4-19.7) |
| Geelhoed; 2013  | System          | <ul style="list-style-type: none"> <li>• Integration</li> <li>• Educational meetings</li> </ul>                                      | Integrated maternal health and HIV care  | Usual Non-integrated care                   | 1) ART in labor: post intervention:112/121 (93%)<br>2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%);<br>3) Infants HIV-positive: post intervention: 9/123 (7%)  | 1) ART in labor: intervention phase =93/96(97%)<br>2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%)<br>3) Infants HIV positive: intervention phase: 7/60(12%)               | 1) 0.96 (0.90-1.02)<br>2) 0.93 (0.88-0.97)<br>3) 0.63 (0.25-1.60)   | --<br>--<br>--   |
| Killam; 2010    | System          | <ul style="list-style-type: none"> <li>• Integration</li> </ul>  | Integration of antenatal   | Usual non-integrated                        | ART initiation during pregnancy: 278/846 (32.9%)   | ART initiation during pregnancy:   | 2.28 (1.86-2.80)  | AOR 2.01 (1.37, 2.95)  |

|                      |        |  |   |                            |  |  |   |  |
|----------------------|--------|--|---|----------------------------|--|--|---|--|
|                      |        |  | and HIV care  | ed care                    |  | 103/716 (14.4%)  |   |  |
| Odeny; 2014          | System | • The use of information and communication technology    | SMS test messages during pregnancy and after delivery             | Usual care                 | 1) Maternal postpartum clinic attendance: 38/194 (19.6%)<br>2) Infant HIV testing by 8 wks: 1172/187 (92.0%)   | 1) Maternal postpartum clinic attendance: 22/187 (11.8%)<br>2) Infant HIV testing by 8 wks: 154/181 (85.1%)  | 1) 1.66 (1.03-2.70)<br>2) 1.08 (1.00-1.16)  | --<br>-  |
| Rotheram-Borus; 2014 | System | • Role expansion or task shifting<br>• Outreach services | Antenatal and postnatal home visits from community health workers | Usual care                 | 1) ART prior to labor: 169/179 (94.4%)<br>2) AZT or HAART during labor: 1164/179 (91.6%)<br>3) NVP or HAART at onset of labor: 166/179 (92.7%)<br>4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%)<br>5) Infant ART after birth: 172/179 (96.1%)<br>6) Infant HIV testing at 6 weeks: 155/160 (96.9%)   | 1) ART prior to labor: 149/159 (93.7%)<br>2) AZT or HAART during labor: 147/159 (92.5%)<br>3) NVP or HAART at onset of labor: 142/159 (89.3%)<br>4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%)<br>5) Infant ART after birth: 142/159 (89.3%)<br>6) Infant HIV testing at 6 weeks: 132/140 (94.3%)  | 1) 1.01 (0.95-1.06)<br>2) 0.99 (0.93-1.06)<br>3) 1.04 (0.97-1.11)<br>4) 1.08 (1.01-1.15)<br>5) 1.08 (1.01-1.14)<br>6) 1.03 (0.98-1.08)  | 1) AOR 1.08 (0.42, 2.80)<br>2) AOR 0.87 (0.39, 1.95)<br>3) AOR 1.52(0.70, 3.31)<br>4) AOR 2.94(1.41, 6.12)<br>5) AOR 2.95 (1.12, 7.73)<br>6) AOR 1.80 (0.62, 5.28)   |
| Rustagi; 2016        | System | • Continuous quality improvement                         | Facility level systems analysis and improvement intervention      | No-intervention            | 1) ART in pregnancy: 575/839 (69%)<br>2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)   | 1) ART in pregnancy: 664/1037(64%)<br>2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)   | 1) 1.07 (1.00-1.14)<br>2) 1.23 (1.09-1.40)  | --<br>--   |
| Turan; 2015          | System | • Integration  | Integrated HIV and antenatal care                                 | Usual, non-integrated care | 1) ART during pregnancy: 138/173 (80%)<br>2) ART during Labor: 28/173 (16%)<br>3) ART after birth: 22/173 (13%)<br>4) Infant ART after birth: 50/173 (29%)<br>5) ART throughout all 3 PMTCT periods: 37/176 (21.0%)<br>6) Infant HIV testing before 3 months: 143/569 (25%)<br>7) Infant HIV testing at 9 months: 361/569 (63%)<br>8) Infants HIV tested by 6 weeks: 143/568 (25%)<br>9) Infants HIV positive at 6 | 1) ART during pregnancy: 75/152 (49%)<br>2) ART during Labor: 84/152 (55%)<br>3) ART after birth: 57/152 (38%)<br>4) Infant ART after birth: 106/152 (70%)<br>5) ART throughout all 3 PMTCT periods: 23/153 (15.0%)<br>6) Infant HIV testing before 3 months: 106/603 (18%)<br>7) Infant HIV testing at 9 months: 326/603 (54%)<br>8) Infants HIV tested by 6 weeks: 106/594 (18%)<br>9) Infants HIV positive at 6 | 1) 1.61 (1.35-1.93)<br>2) 0.29 (0.20-0.42)<br>3) 0.34 (0.22-0.53)<br>4) 0.41 (0.32-0.54)<br>5) 1.40 (0.87-2.24)<br>6) 1.43 (1.14-1.79)<br>7) 1.17 (1.07-1.29)<br>8) 1.41 (1.13-1.76)<br>9) 0.64 (0.22-1.84) | 1) AOR 4.05 (2.0, 8.0)<br>2) AOR 0.16 (0.04, 0.68)<br>3) AOR 0.24 (0.08, 0.70)<br>4) AOR 0.18 (0.09, 0.35)<br>5) AOR 1.72 (0.85, 3.48)<br>6) AOR 1.57 (0.61,4.07)<br>7) AOR 1.47 (0.76,2.86)<br>8) AOR 1.57 (0.61-4.07)<br>9) AOR 0.62 (0.20,1.98)<br>10) AOR 1.45 (0.71,2.82) |

|  |  |  |  |   |  |  |                             |
|--|--|--|--|---|--|--|-----------------------------|
|  |  |  |  | weeks: 16/143<br>(4.2%)<br>10) Infants HIV<br>tested by end of<br>study (up to 12<br>m): 382/568<br>(67.3%)<br>11) Infants HIV<br>positive at 9<br>months: 28/382<br>(7.3%) | weeks: 7/106<br>(6.6%)<br>10) Infants HIV<br>tested by end of<br>study (up to 12<br>m): 338/594<br>(57.0%)<br>11) Infants HIV<br>positive at 9<br>months: 27/338<br>(8.0%) | 10) 1.18 (1.08-<br>1.29)<br><br>11) 0.92 (0.55-<br>1.53) | 11) AOR 0.89<br>(0.56,1.43) |
|--|--|--|--|---|--|--|-----------------------------|

302

303 Findings of the narrative synthesis are outlined below first as intervention types within  
304 intervention target categories (patient, provider, system) and then by PMTCT outcome.

305

306 Synthesis of findings according to intervention type and target:

307 Patient Level Interventions:

308 Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of  
309 bias ranged from 3 to 6 of 6 criteria rated as high or unclear. Ezeanolue et al. (27) included 40  
310 clusters and 3,024 patients and evaluated a complex intervention that included monthly baby  
311 showers at participating churches where expectant mothers participated in educational games,  
312 received 'mama packs' containing supplies needed during delivery (sterile gloves, alcohol  
313 swabs, clean razor, etc.) and laboratory testing, and were given a contact point for follow-up.

314 Women in the intervention group were found to be significantly more likely to complete linkage  
315 to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI  
316 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks  
317 postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided

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2  
3 318 pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at  
4  
5 319 home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss  
6  
7  
8 320 et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT  
9  
10 321 intervention compared to standard care. They found no statistically significant difference in  
11  
12 322 PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant  
13  
14 323 blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and  
15  
16 324 evaluated whether conditional cash transfers improved adherence, acceptance of and retention in  
17  
18 325 PMTCT services to 6 weeks postpartum. They found women in the intervention group were  
19  
20 326 significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have  
21  
22 327 attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95%  
23  
24 328 CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.  
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### 30 31 330 Patient/Provider Level Interventions:

32  
33 331 One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention  
34  
35 332 directed at both patients and providers in which peer mentors were trained to provide in person  
36  
37 333 education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31).  
38  
39 334 They found patients in the intervention group were significantly less likely to adhere to ARTs  
40  
41 335 during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-  
42  
43 336 0.74]). No statistically significant effects were found on the remaining outcomes including: ART  
44  
45 337 use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART  
46  
47 338 post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were  
48  
49 339 unable to reach authors for additional information on long term outcomes.  
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3 341 Provider Level Interventions:  
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5 342 Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day  
6  
7 343 PMTCT knowledge and skills training course for nurses and midwives compared to standard  
8  
9 344 training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They  
10  
11 345 found a statistically significant increase in the proportion of women with ART detected in cord  
12  
13 346 blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).  
14  
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19 348 Provider/System Level Interventions:  
20

21 349 Five studies reported interventions directed at both the provider and health system level  
22  
23 350 (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-  
24  
25 351 Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated  
26  
27 352 transmission of HIV test results to clinic staff via short message service (SMS), and ongoing  
28  
29 353 support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring  
30  
31 354 and addressing clinic underperformance). There was a trend towards an increase in the  
32  
33 355 proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.  
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40 357 Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess  
41  
42 358 the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing  
43  
44 359 (MIP+SMS) combined with integrated care against standard care (SOC). They found no  
45  
46 360 significant difference in maternal retention in care at 12 months in either intervention group  
47  
48 361 relative to controls using study definitions, or ministry of health definitions for retention. They  
49  
50 362 found no statistically significant difference in infant retention in care at 12 months in either  
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363 intervention group relative to controls using study definitions, or ministry of health definitions  
364 for retention .

365  
366 Oyeledun et al. (35) compared a continuous quality improvement intervention including  
367 coaching visits and collaborative meetings to standard ministry of health support in 32 clusters  
368 and 511 patients. They found no significant difference in retention in care at 6 months, in  
369 initiation of ART prophylaxis in infants within 72 hours of birth, or in proportion of women  
370 initiated on ARTs within 2 weeks of enrolment. They found significantly improved rates of  
371 infant HIV testing at 6-10 weeks (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-  
372 2.42]).

373  
374 Phiri et al. (36) conducted a 3-arm cluster RCT with 21 clusters and 1269 women evaluating  
375 facility-based peer support (FBPS) and community-based peer support (CBPS) from expert  
376 mothers against standard of care (SOC). They found non-significant improvement with FBPS  
377 and small statistically significant improvements with CBPS in uptake of ARTs (RR= 1.12 [95%  
378 CI 1.06-1.18]; ARD 0.09 [95% CI 0.01-0.18]), retention in care at 1 year (RR=1.01 [95% CI  
379 0.92-1.10]; ARD= 0.08 [95% CI 0.04-0.20]), and retention in care at 2 years (RR= 1.42 [95% CI  
380 1.22-1.65]; ARD=0.16 [95% CI 0.03-0.30]), relative to SOC. Retention in care at 2 years was  
381 significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-  
382 1.43]) using ministry of health definitions for retention in care. Infant HIV testing at 6 weeks was  
383 significantly higher in the CBPS only (RR=1.23 [95% CI 1.11-1.38]). There was no difference in  
384 infant HIV positive rates at 6 weeks in either intervention group.

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3 386 Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased  
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5 387 training of community health workers and increased home visits by community health workers  
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7 388 during and post delivery to provide PMTCT counselling and newborn care. They found a  
8  
9 389 significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention  
10  
11 390 group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in  
12  
13 391 mother to child HIV transmission at 12 weeks.  
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### 19 393 System Level Interventions:

21 394 Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias  
22  
23 395 ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or  
24  
25 396 unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services  
26  
27 397 including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and  
28  
29 398 community involvement through male champions, compared to standard care across 12 clusters  
30  
31 399 and 369 patients. They found significant improvement in the proportion of eligible women  
32  
33 400 started on ART for PMTCT (RR= 2.47 [95% CI 2.07-2.95]; ARR 3.3 [95% CI 1.4-7.8]), and in  
34  
35 401 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI  
36  
37 402 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-  
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39 403 19.7]).  
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47 405 Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and  
48  
49 406 evaluated the impact of integration of HIV and maternal child health services during both  
50  
51 407 antenatal and postnatal periods. They found no improvement in the proportion of women  
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3 408 receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48  
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5 409 hours and the proportion of HIV positive infants.  
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10 411 Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual  
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12 412 care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a  
13  
14 413 statistically significant increase in the proportion of eligible women receiving ARTs during  
15  
16 414 pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).  
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21 416 Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during  
22  
23 417 pregnancy and post-delivery. They found statistically significant improvements in maternal  
24  
25 418 antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks  
26  
27 419 (RR= 1.08 [1.00-1.16]).  
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33 421 Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in  
34  
35 422 addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in  
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37 423 the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14];  
38  
39 424 AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the  
40  
41 425 intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no  
42  
43 426 significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal  
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45 427 NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.  
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3 429 Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters  
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5 430 in 3 countries, including 1876 patients. They found no significant improvement in the proportion  
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7 431 of pregnant women receiving ARTs.  
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10 432  
11  
12 433 Turan et al. (25) included 12 clusters and 1172 patients and examined the effects of integration  
13  
14 434 of HIV and antenatal care compared with standard non-integrated care. Self-reported maternal  
15  
16 435 ART use across the PMTCT spectrum, pre, during, and post delivery, was not significantly  
17  
18 436 different between groups, although it was significantly higher during pregnancy (RR=  
19  
20 437 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]). ART use was significantly lower among  
21  
22 438 intervention sites during labor delivery RR=-0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI  
23  
24 439 0.04, 0.68] and post-delivery (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]). Infant  
25  
26 440 ART use after birth was significantly lower in intervention sites (RR= 0.41 [95% CI 0.32-0.54];  
27  
28 441 AOR= 0.18 [95% CI 0.09-0.35]), although infant HIV testing was increased at 6 weeks, and 9  
29  
30 442 months in intervention sites, the difference was not statistically significant. No difference was  
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32 443 found for infant HIV infection rates at 6 weeks, or 9 months.  
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40 445 Synthesis of findings according to PMTCT outcomes:  
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42 446 The vast majority of studies reported short-term PMTCT outcomes with ART use during  
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44 447 pregnancy (10/18) and labor and delivery (6/18), infant prophylaxis at birth (6/18), and infant  
45  
46 448 HIV testing at 6-10 weeks (5/18). Overall, findings are often mixed and effect sizes small, with  
47  
48 449 many of uncertain clinical significance. For example, 5 studies found significant improvements  
49  
50 450 in ART use during pregnancy ranging with RR ranging from 1.12 to 2.48 (25, 26, 27, 36, 38), 4  
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52 451 found no significant difference (33, 35, 41, 42) and 1 found significantly reduced ART use  
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3 452 during pregnancy in the control group (31). Findings for ART use during labor and delivery were  
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5 453 again mixed, with 4/6 finding no significant effect (29, 31, 39, 41)), 1 finding a significant but  
6  
7 454 small improvement RR=1.17 (32) and 1 finding significantly reduced ART use in the  
8  
9 455 intervention group RR=1.614 (25). Findings for infant prophylaxis at birth and infant HIV  
10  
11 456 testing by 6-10 weeks are similarly mixed. One of 6 studies reported a small significant  
12  
13 457 improvement in infant HIV prophylaxis at birth -RR=1.08 ( 41), 1/6 significantly reduced infant  
14  
15 458 prophylaxis at birth RR=0.41 (25) and 4/6 studies finding no significant difference (28, 31, 35,  
16  
17 459 39). Three of 6 found significantly improved rates of infant testing by 6-10 weeks of age with  
18  
19 460 RR ranging from 1.08 to 1.93 (35,37,40) and 2/6 no difference (25, 41).  
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21  
22 461 Only 1 study evaluated ART use in the post-partum period and again found a significantly  
23  
24 462 reduced ART use during this period RR=0.34 (25).Two additional studies evaluated uptake  
25  
26 463 across the cascade, with 1/2 finding significantly improved uptake RR= 1.26 (30) and 1/2 finding  
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28 464 no difference (25).  
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35 466 Outcome definitions for retention in care and infant HIV-positive rates were highly variable,  
36  
37 467 ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other  
38  
39 468 PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for  
40  
41 469 retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant  
42  
43 470 retention in care at 6 weeks, with 2 studies finding significantly improved retention with RR  
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45 471 ranging from 1.11 to 9.44 (30, 38) and the third finding no difference (27).Three studies  
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47 472 examined infant HIV-positive rates at 6 weeks post-partum, all found no difference.  
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54 474 **Discussion:**  
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3 475 Eighteen studies were included in our review. Heterogeneity of interventions and outcome  
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5 476 reported limited both comparison across studies and intervention categories, as well as,  
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7 477 opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias,  
8  
9 478 primarily due to limitations inherent to health systems research and unclear reporting of key  
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11 479 methodological factors.  
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17 481 Based on our review findings, several interventions appear promising. In the single meta-  
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19 482 analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use  
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21 483 during pregnancy with integration of HIV and antenatal care compared to standard non-  
22  
23 484 integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies  
24  
25 485 found small positive effects of integration of HIV and antenatal care, alone or as part of a  
26  
27 486 complex intervention, on ART use during pregnancy. However, not all studies or all outcomes in  
28  
29 487 some included studies showed significant benefit with integration of ANC and HIV. Therefore,  
30  
31 488 as integrated care is increasingly common future work focusing on how integration of ANC and  
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33 489 HIV care may be optimized alone or in combination with other interventions to optimize  
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35 490 PMTCT outcomes is needed.  
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42 492 Four studies evaluating different approaches to outreach services alone or in combination with  
43  
44 493 other interventions found small positive effects on linkage to care, ART use during pregnancy  
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46 494 and labor/delivery, and early infant HIV testing. Two studies found positive effects of role  
47  
48 495 expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy  
49  
50 496 and, when combined with outreach services, positive effects were seen on long term retention in  
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52 497 care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT  
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3 498 outcomes, each in a single study, included: educational meetings, conditional cash transfers,  
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5 499 continuous quality improvement, and use of information and communication technology.  
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10 501 An important finding of the present review is the high degree of variability in outcome  
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12 502 definitions and relative lack of longer-term outcome data. While in some instances variability of  
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14 503 outcome definitions may be considered a strength where both self-report and biological markers  
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16  
17 504 of ART use are included, variability in timing of outcomes limits comparison across studies and  
18  
19 505 opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the  
20  
21 506 findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is  
22  
23 507 clearly critical to reducing HIV transmission, longer term outcomes are equally important to  
24  
25 508 understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of  
26  
27 509 future work would be substantially improved through both standardization of timing of PMTCT  
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29 510 outcomes and through funding opportunities that would allow for evaluation of longer term  
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31 511 outcomes.  
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38 513 In keeping with other systematic reviews focused on interventions aimed at improving PMTCT  
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40 514 care and outcomes published to date (8,9,13,14,15), our review found the evidence base available  
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42 515 to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor  
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45 516 Car et al. (9), which included a single study and found -improved ART use in labor/delivery from  
46  
47 517 integration of care, our single meta-analysis including 2 studies found a positive effect of  
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49 518 integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only  
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51 519 2 of which met inclusion criteria for the present review, and they also found variable effects of  
52  
53 520 non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al.  
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3 521 (14) included 10 articles, with 2 overlapping studies included in our review, and focused on  
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5 522 postpartum retention of women in PMTCT and ART care. This latter review, which included  
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7 523 both high and LMICs and a broader range of study designs, focused on a limited portion of the  
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9 524 PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone  
10  
11 525 interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to  
12  
13 526 improve PMTCT service delivery and promote retention. Their review was conducted over a  
14  
15 527 similar timeframe to the present review, however, it differs from the present review in its  
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17 528 inclusion of high income country studies, inclusion of a range of study designs, and in its  
18  
19 529 approach to categorization of interventions. Thirty-four studies were included in their review, 11  
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21 530 of which were included in the present review. They found weak evidence for improvement of  
22  
23 531 early infant HIV diagnosis from mobile-phone based interventions and for male involvement in  
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25 532 reducing infant HIV transmission.  
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33 534 Given the focus of the present review on providing evidence-based guidance to PMTCT program  
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35 535 planners and implementers based LMICs our review differs from the reviews noted above in  
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37 536 several ways. First, to optimize the quality of evidence we limited our review to randomized and  
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39 537 non-randomized controlled trials and interrupted times series studies. Second, to increase the  
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41 538 applicability of findings to LMIC implementers, we limited our review to studies conducted in  
42  
43 539 LMICs. Third, we included a broad range of intervention categories and included both maternal  
44  
45 540 and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to  
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47 541 provide information of direct relevance to implementation planning, we categorized and  
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49 542 analyzed interventions at both the level at which they are implemented (patient, provider,  
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3 543 system) and using the EPOC intervention classification scheme, which groups interventions  
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5 544 based on the intervention process/activities employed.  
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12 547 Limitations:  
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14 548 While agreement on data extraction was not calculated, an initial calibration exercise was carried  
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16 549 out to ensure consistency in data extraction. Following this, comparison of completed data  
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18 550 extraction forms revealed few differences. Although no study was excluded for language, it is  
19  
20 551 possible that use of translation software may have resulted in exclusion of an eligible study due  
21  
22 552 to inaccurate translation. Additionally, while unlikely to have led to a significant difference in  
23  
24 553 results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO  
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26 554 as the later was not accessible to the second information technologist.  
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33 556 The multifaceted nature of the majority of interventions evaluated and variability in PMTCT  
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35 557 outcomes reported, limited our ability to combine studies statistically. In addition, efforts to  
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37 558 contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due  
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39 559 to the small number of studies included in the meta-analysis publication bias could not be  
40  
41 560 examined. Additionally, although pre-specified in our protocol, interpretation of findings, most  
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43 561 commonly infant HIV infection rates, are limited by lack of power to assess secondary outcomes  
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45 562 among included studies. As 7 of the 18 studies limited participation to women 17-18 years of age  
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47 563 or older, results may be less generalizable to younger mothers. Finally, although the EPOC  
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49 564 search filter is designed to identify articles from all low- and middle-income countries, only  
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51 565 articles from Sub-Saharan Africa were included in the review. Results therefore may be less  
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3 566 generalizable to LMICs outside Sub-Saharan Africa. In addition, this finding highlights  
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5 567 limitations in the evidence to date and where funding should be targeted for future research  
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8 568 based on knowledge users needs.  
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12 570 *Future Directions:*

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14 571 Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were  
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16 572 generally small and often mixed across studies, and based on a small number of studies that were  
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18 573 largely at moderate to high risk of bias. Further research is needed both to improve quantity and  
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20 574 quality of data. First, replication of promising approaches is needed. Second, improved  
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22 575 publication reporting to ensure key methodological factors are addressed and to provide detail on  
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24 576 the likely impact of factors that cannot be modified through design. This transparency in  
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26 577 reporting will enhance interpretation and utility of findings in informing PMTCT policy and  
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28 578 program decision making. For example, while the nature of designs for evaluating PMTCT  
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30 579 interventions, often make blinding of participants impossible, description of the context and  
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32 580 likely impact would aid interpretation. Additionally, use of blinded outcome assessment or  
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34 581 objective outcomes such as laboratory confirmation of ART in blood samples will increase study  
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36 582 impact. Third, given the inherent difficulties in evaluating complex interventions, increased use  
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38 583 of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would  
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40 584 be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade and  
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42 585 longer term outcomes in particular where feasible, would allow for increased comparison across  
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44 586 interventions.  
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54 588 **Conclusions:**  
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3 589 The body of evidence synthesized in this review and in the literature to date on effectiveness of  
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5 590 interventions to improve uptake and retention of mothers and infants in PMTCT care is limited  
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8 591 by low quality evidence. A single meta-analysis of 2 studies employing integration of antenatal  
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10 592 and HIV care suggested a potential for improvement of ART use during pregnancy based on  
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12 593 weak evidence. Overall findings are mixed and effect sizes small and of uncertain clinical  
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14 594 significance. In order to improve the utility of evidence to program planners future studies  
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16  
17 595 should strive to include key outcomes across the range of the PMTCT cascade where feasible,  
18  
19 596 reduce risk of bias where possible and improve reporting of key methodological factors to allow  
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21  
22 597 for improved assessment of risk of bias and understanding of the likely impact of risk of bias  
23  
24 598 where it cannot be addressed in design.  
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28 600 **List of abbreviations:** ANC: Antenatal care; ART: Anti-Retroviral Therapy; AZT: Zidovudine,  
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30 601 EPOC: Effective Practice and Organization of Care; HAART: Highly active antiretroviral  
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32 602 therapy, HIV: Human Immunodeficiency Virus; LMIC: Low and Middle Income Country;  
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34 603 MeSH: Medical Subject Headings; MOH: Ministry of Health; NVP: Nevirapine, PMTCT:  
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36 604 Prevention of mother to child transmission of HIV; RCT: Randomized controlled trial; SMS:  
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38 605 Short message service; SOC: Standard care; Versus: vs.  
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45 607 **Declarations:**

46  
47 608 **Ethics approval and consent to participate:** Not applicable.  
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49 609 **Consent for publications:** Not applicable.  
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51 610 **Availability of data and material:** No additional data available.  
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8  
9 614 under Grant K99 MH104154-01A1 and the National Institute of Allergies and Infectious  
10  
11 615 Diseases (P30 AI50410 and R01 AI131060-01).  
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13

14 616 **Competing Interests:** The authors have declared that no competing interests exist. The authors  
15  
16 617 alone are responsible for the writing and content of the paper.  
17  
18  
19 618

20  
21 619 **Authors' contributions:** LPR and MvL conceived the study. LPR and SS developed the search  
22  
23 620 strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of  
24  
25 621 article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence  
26  
27 622 tables and manuscript. LPR conducted the meta-analysis with support from BP, MCH, NER, SP,  
28  
29 623 ML, and FC provided content expertise and assisted with preparation of the protocol and  
30  
31 624 manuscript. All authors provided critical revision of the manuscript and read and approved the  
32  
33 625 final manuscript.  
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41  
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31 804 **Captions for appended Tables and Figures:**  
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35 806 Table 1: Characteristics of Included Studies  
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37 807 Table 2: Results of Included Studies  
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39 808 Figure 1: PRISMA diagram of search results and screening  
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41 809 Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to  
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43 810 usual (non-integrated care) effect on ART use during pregnancy  
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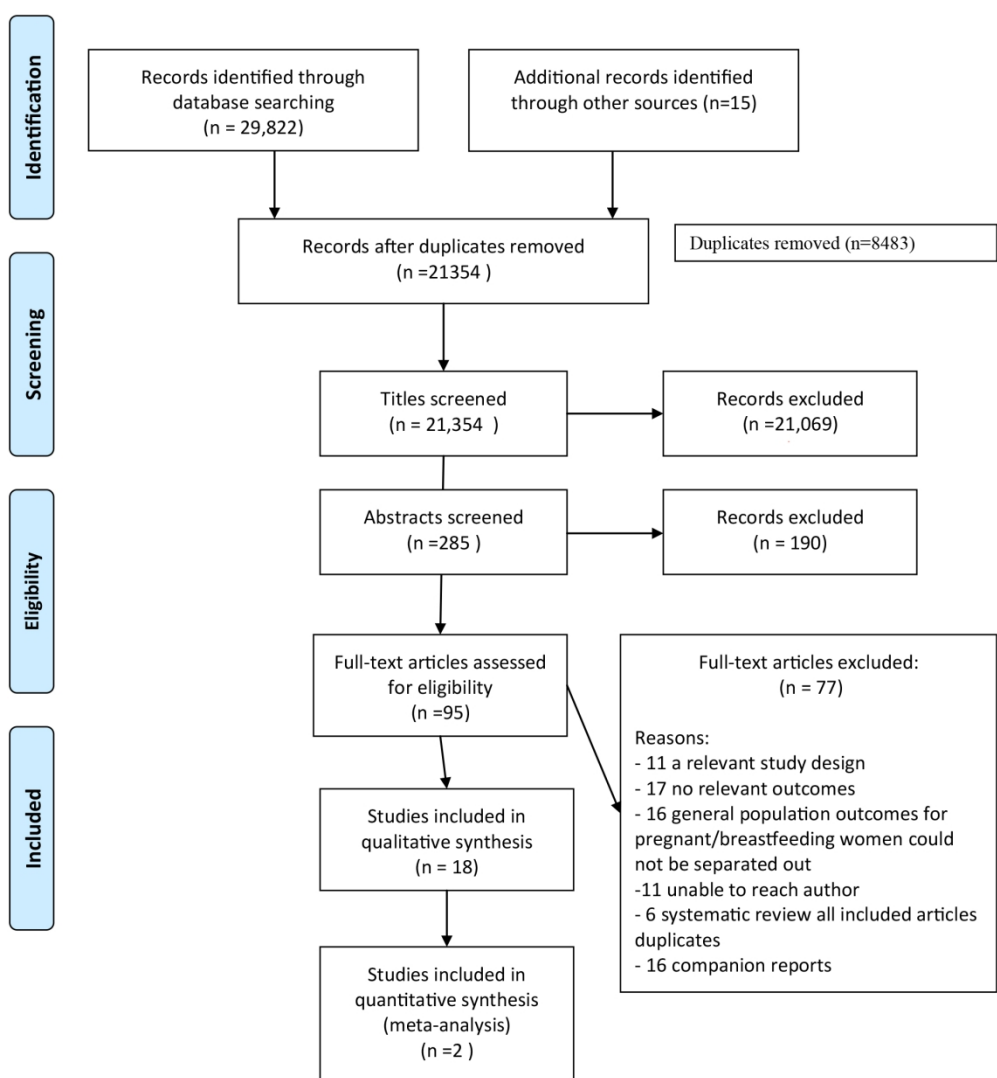


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

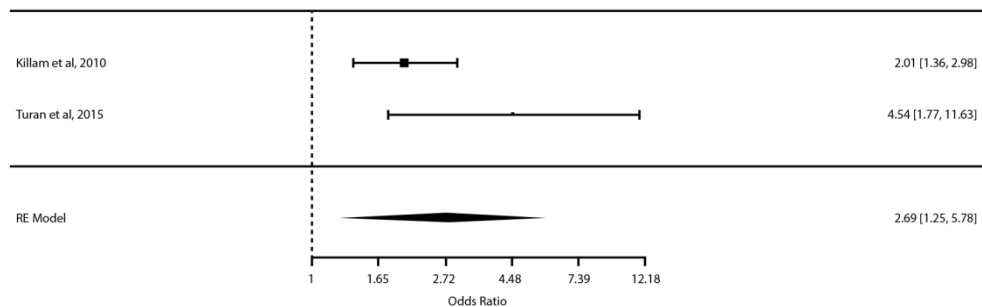
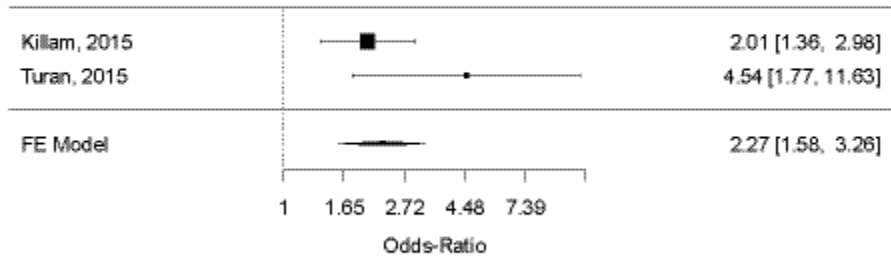


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

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8 Pregnant / Breastfeeding Women

- 9 1 Pregnant Women/ (5226)  
10 2 exp Breast Feeding/ (26666)  
11 3 Milk, Human/ (15697)  
12 4 Infectious Disease Transmission, Vertical/ (12256)  
13 5 fetus/ (68631)  
14 6 exp pregnancy/ (723003)  
15 7 peripartum period/ (427)  
16 8 exp Postpartum Period/ (49233)  
17 9 exp pregnancy complications/ (345863)  
18 10 exp Maternal Health Services/ (35913)  
19 11 pregnan\*.mp,kw,kf. (778553)  
20 12 gestat\*.tw,kw,kf. (144054)  
21 13 breastfeed\*.mp,kw,kf. (13469)  
22 14 (breast adj2 feed\*).mp,kw,kf. (30938)  
23 15 (breast adj2 milk).mp,kw,kf. (8972)  
24 16 breastmilk.tw,kw,kf. (683)  
25 17 human milk.tw,kw,kf. (7840)  
26 18 lactat\*.mp,kw,kf. (165010)  
27 19 (milk adj2 eject\*).tw,kw,kf. (704)  
28 20 (milk adj2 let\*-down).tw,kw,kf. (68)  
29 21 ((expectant or expecting) adj2 wom#n).mp,kw,kf. (182)  
30 22 parturit\*.tw,kw,kf. (11506)  
31 23 birth\*.mp,kw,kf. (259925)  
32 24 childbirth\*.mp,kw,kf. (14074)  
33 25 child-birth\*.mp,kw,kf. (491)  
34 26 deliver\*.mp,kw,kf. (474171)  
35 27 puerper\*.mp,kw,kf. (21074)  
36 28 breastfed.tw,kw,kf. (3524)  
37 29 mtct.tw,kw,kf. (559)  
38 30 pmtct.tw,kw,kf. (725)  
39 31 (vertical adj2 transmission\*).tw,kw,kf. (4511)  
40 32 f?etus\*.mp,kw,kf. (137278)  
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4 34 (breast adj2 fed\*).tw,kw,kf. (5276)  
5 35 in-utero.tw,kw,kf. (20490)  
6 36 (intrauterine or intra-uterine).tw,kw,kf. (42420)  
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8 37 (trans-placent\* or transplacent\*).tw,kw,kf. (5212)  
9 38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)  
10 39 (parent\* adj2 (child\* or infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (28605)  
11 40 mother\*.tw,kw,kf. (147803)  
12 41 (nursing adj2 (infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (1319)  
13 42 (prenatal\* or pre-natal\*).tw,kw,kf. (70920)  
14 43 (perinatal\* or peri-natal\*).tw,kw,kf. (51747)  
15 44 (post-natal\* or postnatal\*).tw,kw,kf. (85370)  
16 45 (antenatal\* or antenatal\*).tw,kw,kf. (23135)  
17 46 (antepartum\* or ante-partum\*).tw,kw,kf. (4566)  
18 47 (postpartum\* or post-partum\*).tw,kw,kf. (40829)  
19 48 maternal\*.tw,kw,kf. (172644)  
20 49 or/1-48 (1763167)  
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#### 30 HIV/AIDS

- 31 50 exp HIV Infections/ (233689)  
32 51 exp HIV/ (83825)  
33 52 HIV Long-Term Survivors/ (607)  
34 53 AIDS Serodiagnosis/ (6107)  
35 54 hiv.mp,kw,kf. (263320)  
36 55 Human T-Cell Leukemia Virus.mp,kw,kf. (2850)  
37 56 htlv-iii.mp,kw,kf. (1652)  
38 57 (acquired adj2 immun\* adj2 (syndrome\* or virus\*)).mp,kw,kf. (86030)  
39 58 (human\* adj2 immun\* adj2 deficien\* adj2 virus\*).mp,kw,kf. (491)  
40 59 (human\* adj2 immun\* adj2 virus\*).mp,kw,kf. (76929)  
41 60 (syndrome\* adj2 lymphadenopath\*).tw,kw,kf. (335)  
42 61 slim disease.tw,kw,kf. (25)  
43 62 lymphadenopathy-associated virus\*.mp,kw,kf. (295)  
44 63 lav-htlv-iii.mp,kw,kf. (211)  
45 64 sbl-6669.mp,kw,kf. (16)  
46 65 lav-2.mp,kw,kf. (25)  
47 66 (acquired adj2 immun\* adj2 deficien\* adj2 syndrome\*).tw,kw,kf. (5057)  
48 67 (aids adj10 (disease\* or syndrome\*)).mp,kw,kf. (27876)  
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3 68 (aids adj1 related).tw,kw,kf. (6614)

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5 69 htlv\*.tw,kw,kf. (11427)

6  
7 70 hiv###mp,kw,kf. (1760)

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9 71 or/50-70 (325026)

10  
11 Patient uptake / dropouts / participation

12 72 Patient Dropouts/ (6786)

13 73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)

14 74 exp Consumer Participation/ (32566)

15 75 dropout\*.tw,kw,kf. (6483)

16 76 (uptake or up-take).tw,kw,kf. (248330)

17 77 (drop\* adj1 out\$1).tw,kw,kf. (8228)

18 78 (refusal\* or refuse\$1 or refusing).tw,kw,kf. (23366)

19 79 (patient\* adj2 (elope or elope\$1 or eloping)).tw,kw,kf. (4)

20 80 (non complian\* or noncomplian\*).tw,kw,kf. (9990)

21 81 complian\*.tw,kw,kf. (84306)

22 82 (uncooperat\* or unco-operat\* or un-co-operat\*).tw,kw,kf. (1028)

23 83 (cooperat\* or co-operat\*).tw,kw,kf. (102475)

24 84 (non-accept\* or nonaccept\*).tw,kw,kf. (592)

25 85 accept\*.tw,kw,kf. (279089)

26 86 (nonparticipat\* or non-participat\*).tw,kw,kf. (1298)

27 87 participat\*.tw,kw,kf. (322007)

28 88 (nonadher\* or non-adher\*).tw,kw,kf. (10638)

29 89 adher\*.tw,kw,kf. (114637)

30 90 (retain\* or retention\*).tw,kw,kf. (244370)

31 91 (non-attend\* or nonattend\*).tw,kw,kf. (1453)

32 92 attend\*.tw,kw,kf. (110407)

33 93 (comply\* or complies or complian\*).tw,kw,kf. (91550)

34 94 (non-comply\* or noncomply\* or non-complian\* or noncomplian\*).tw,kw,kf. (10004)

35 95 reluctan\*.tw,kw,kf. (8504)

36 96 ((healthcare or care or advice or medical or information) adj3 seek\$3).tw,kw,kf. (15252)

37 97 (disengag\* or dis-engag\*).tw,kw,kf. (2812)

38 98 engag\*.tw,kw,kf. (82419)

39 99 avoid\*.tw,kw,kf. (237366)

40 100 ut.fs. (144195)

41 101 ignor\*.tw,kw,kf. (27215)

42 102 reject\*.tw,kw,kf. (82472)

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3 103 (non-embrac\* or nonembrac\*).tw,kw,kf. (0)  
4 104 (un-embrac\* or unembrac\*).tw,kw,kf. (1)  
5 105 (embrace\* or embracing).tw,kw,kf. (7691)  
6 106 (un-accept\* or unaccept\*).tw,kw,kf. (14546)  
7 107 (unadher\* or un-adher\*).tw,kw,kf. (14)  
8 108 no-show\*.tw,kw,kf. (484)  
9 109 (follow\* adj1 up).tw,kw,kf. (638770)  
10 110 incent\*.tw,kw,kf. (17823)  
11 111 enabl\*.tw,kw,kf. (214935)  
12 112 disincent\*.tw,kw,kf. (859)  
13 113 utiliz\*.tw,kw,kf. (319558)  
14 114 (inclin\* or disinclin\*).tw,kw,kf. (12034)  
15 115 or/72-114 (2984236)  
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24 Study type / characteristics  
25 116 randomized controlled trial.pt. (387105)  
26 117 exp Randomized controlled trial/ (387132)  
27 118 exp Randomized Controlled Trials as Topic/ (97414)  
28 119 clinical trial.pt. (490674)  
29 120 Double-Blind Method/ (128228)  
30 121 Placebos/ (32662)  
31 122 clinical trials as topic/ (171490)  
32 123 evaluation research/ (119973)  
33 124 program evaluation/ (47548)  
34 125 Feasibility Studies/ (45412)  
35 126 Pilot Projects/ (85700)  
36 127 Evaluation Studies as Topic/ (119973)  
37 128 Cost-Benefit Analysis/ (61646)  
38 129 (random\* or non-random\* or unrandom\* or nonrandom\*).mp,kw,kf. (874470)  
39 130 placebo\*.mp,kw,kf. (168179)  
40 131 rct\*1.tw,kw,kf. (17367)  
41 132 ((singl\* or doubl\* or trebl\* or tripl\*) adj1 (mask\* or blind\* or dumm\*)).mp,kw,kf. (176744)  
42 133 evaluat\*.mp,kw,kf. (2416275)  
43 134 effectiv\*.mp,kw,kf. (1149619)  
44 135 sustainab\*.mp,kw,kf. (23041)  
45 136 feasib\*.mp,kw,kf. (177882)  
46 137 appropriateness.mp,kw,kf. (12458)  
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3 138 efficac\*.mp,kw,kf. (507876)  
4 139 impact\*.mp,kw,kf. (537916)  
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6 140 (pilot adj2 (project\* or study or studies)).mp,kw,kf. (103303)  
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8 141 cost-effectiv\*.mp,kw,kf. (73309)  
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10 142 (cost\*1 adj2 benefit\*1).mp,kw,kf. (69472)  
11 143 (interrupt\* adj2 time).mp,kw,kf. (1224)  
12 144 or/116-143 (4705604)  
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14 Lower middle income countries

- 15 145 Developing Countries/ (63034)  
16 146 (Imic or Imics or lami countr\*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)  
17 147 ((developing or less\* developed or under developed or underdeveloped or middle income  
18 or low\* income or underserved or under served or deprived or poor\*) adj (countr\* or nation? or  
19 population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)  
20 148 (Afghan\* or Albania\* or Algeria\* or Angola\* or Antigua\* or Barbud\* or Argentin\* or  
21 Armenia\* or Aruba\* or Azerbaijan\* or Bahrain\* or Bangladesh\* or Barbad\* or Benin\* or Byelarus\*  
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25 Cameroon\* or Cameron\* or Cape Verde\* or Central African Republic or Chad\* or Chile\* or China  
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3 Roumania\* or Russia\* or Rwanda\* or Ruanda\* or Saint Kitts\* or St Kitts or Nevis\* or Saint Lucia\*  
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5 Tome\* or Saudi Arabia\* or saudi or Senegal\* or Serbia\* or Montenegr\* or Seychelles or Sierra  
6 Leone or Slovenia\* or Sri Lanka\* or Ceylon\* or Solomon Islands or Somalia\* or South Africa\* or  
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11 Venezuela\* or Vietnam\* or Viet Nam\* or West Bank or Yemen\* or Yugoslavia\* or Zambia\* or  
12 Zimbabw\* or Rhodesia\* or cabo verd\*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)  
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18 149 or/145-148 (4677916)  
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21 Full topic

22 150 49 and 71 and 115 and 144 and 149 (3309)

23 151 exp animals/ not (exp animals/ and exp humans/) (4003250)

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26 Full topic minus animal-only studies

27 152 150 not 151 (3291)  
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## Risk of Bias within included studies

| Study                 | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting |
|-----------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|-----------------------------|
| Aliyu; 2016           | Low                        | Unclear                | High                                   | High                           | Low                     | Low                         |
| Dryden-Peterson; 2015 | Unclear                    | Low                    | High                                   | High                           | High                    | Low                         |
| Ezeanolue; 2015       | Low                        | Low                    | High                                   | Unclear                        | High                    | Low                         |
| Geelhoed; 2013        | Unclear                    | Unclear                | Unclear                                | Unclear                        | High                    | High                        |
| Kieffer; 2011         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Killam; 2010          | Unclear                    | High                   | High                                   | Unclear                        | High                    | Unclear                     |
| Mwapasa; 2017         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Low                         |
| Odeny; 2014           | Low                        | Low                    | High                                   | Unclear                        | Low                     | Unclear                     |
| Oyeledun; 2017        | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Phiri; 2017           | Unclear                    | High                   | High                                   | Low                            | Low                     | Low                         |
| Reynolds; 2010        | Unclear                    | Unclear                | High                                   | High                           | High                    | Unclear                     |
| Richter; 2014         | Unclear                    | High                   | High                                   | High                           | High                    | Low                         |
| Rotheram-Borus; 2014  | Unclear                    | Unclear                | High                                   | High                           | Unclear                 | Low                         |
| Rustagi; 2016         | Low                        | Unclear                | Unclear                                | Unclear                        | Unclear                 | Low                         |
| Tomlinson; 2014       | Low                        | Unclear                | High                                   | Low                            | Low                     | Low                         |
| Turan; 2015           | Low                        | High                   | High                                   | High                           | High                    | Low                         |
| Weiss; 2014           | Unclear                    | Unclear                | Unclear                                | Unclear                        | Unclear                 | High                        |
| Yotebieng; 2016       | Low                        | Unclear                | High                                   | High                           | High                    | High                        |



# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page # |
|------------------------------------|----|---|--------------------|
| <b>TITLE</b>                       |    |   |                    |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | 1                  |
| <b>ABSTRACT</b>                    |    |   |                    |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4                |
| <b>INTRODUCTION</b>                |    |   |                    |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | 5-6                |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 6                  |
| <b>METHODS</b>                     |    |   |                    |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | 7                  |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 7                  |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 8                  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | 8                  |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 8-9                |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 8-9                |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | 9                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 10                 |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | 10                 |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.   | 10                 |





# PRISMA 2009 Checklist

Page 1 of 2

| Section/topic                 | #  | Checklist item   | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | 10                 |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | N/A                |
| <b>RESULTS</b>                |    |  |                    |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Figure 1           |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | 11-12<br>Table 1   |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 12-13<br>Table 2   |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 14-20<br>Table 3   |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 13<br>Figure 2     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 10                 |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | N/A                |
| <b>DISCUSSION</b>             |    |  |                    |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | 20-23              |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 4, 23              |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 24                 |
| <b>FUNDING</b>                |    |  |                    |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | 25                 |



# PRISMA 2009 Checklist

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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

# BMJ Open

## 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-024907.R2   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 21-Feb-2019  |
| Complete List of Authors:       | Puchalski Ritchie, LM; University of Toronto, Department of Medicine, Division of Emergency Medicine; Li Ka Shing Knowledge Institute, St. Michael's Hospital, Knowledge Translation Program<br>van Lettow, Monique; Dignitas International; University of Toronto Dalla Lana School of Public Health<br>Pham, Ba; Li Ka Shing Knowledge Institute, St. Michael's Hospital<br>Straus, Sharon; St. Michael's Hospital, Li Ka Shing Knowledge Institute; University of Toronto, Department of Medicine<br>Hosseinipour, Mina C.; University of North Carolina, Division of Infectious Disease; University of North Carolina Project<br>Rosenberg, Nora; University of North Carolina; University of North Carolina Project<br>Phiri, Sam; University of North Carolina, Department of Health Behavior, School of Public Health; Lighthouse Trust<br>Landes, Megan; University Health Network, Department of Emergency Medicine; University of Toronto, Department of Family and Community Medicine<br>Cataldo, Fabian; Dignitas International; University of Toronto, Dalla Lana School of Public Health |
| <b>Primary Subject Heading</b>: | HIV/AIDS   |
| Secondary Subject Heading:      | HIV/AIDS   |
| Keywords:                       | HIV, prevention of mother to child transmission, interventions, uptake, retention  |
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1        **What interventions are effective in improving uptake and retention of HIV-positive**  
2        **pregnant and breastfeeding women and their infants in prevention of mother to child**  
3        **transmission care programs in low- and middle- income countries? A systematic review**  
4        **and meta-analysis**

6        Lisa M. Puchalski Ritchie<sup>1,2,3</sup>, Monique van Lettow<sup>4,5</sup>, Ba Pham<sup>2</sup>, Sharon E. Straus<sup>1,2</sup>, Mina C.  
7        Hosseinipour<sup>6,7</sup>, Nora E. Rosenberg<sup>6,7,8</sup>, Sam Phiri <sup>6,9,10,11</sup>, Megan Landes<sup>3,4,12</sup>, Fabian Cataldo<sup>4,5</sup>;

8        For the PURE consortium

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27 34 Fabian Cataldo: f.cataldo@dignitasinternational.org  
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## Abstract

### Objective:

This review was conducted to identify interventions effective in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services in LMICs in order to inform program planning.

### Methods:

We conducted a systematic review of studies comparing usual care to any intervention to improve uptake and retention of HIV-positive pregnant or breastfeeding women and their children from birth to 2 years of age in PMTCT services in LMICs. Twenty-two electronic databases were searched from inception to January 15, 2018, for randomized, quazi-randomized, and non-randomized controlled trials, and interrupted time series studies; reference lists of included articles were searched for relevant articles. Risk of bias was assessed using the Cochrane Effective Practice and Organisation of Care Group criteria. Random effects meta-analysis was conducted for studies reporting similar interventions and outcomes.

### Results:

We identified 29,837 articles of which 18 studies were included in our review. Because of heterogeneity in interventions and outcome measures, only 1 meta-analysis of 2 studies and 1 outcome was conducted; we found a statistically significant increase in ART use during pregnancy for integration of HIV and antenatal care relative to standard non-integrated care (pooled AOR=2.69; 95% CI 1.25-5.78, P=0.0113). The remaining studies assessing other individual, provider, or health system interventions were synthesized narratively with small effects seen across intervention categories for both maternal and infant PMTCT outcomes based predominately on evidence with moderate to high risk of bias.

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2  
3 **69 Conclusions:**  
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6 70 The evidence on effectiveness of interventions to improve uptake and retention of mothers and  
7  
8 71 infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal  
9  
10 72 care may improve ART use during pregnancy. Future studies to replicate promising approaches  
11  
12 73 are needed. Improved reporting of key methodological criteria will facilitate interpretation of  
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14 74 findings and improve the utility of evidence to PMTCT program planners.

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17 75 **Systematic review registration:** PROSPERO-CRD42015020829  
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19 76 **Key Words:** HIV, prevention of mother to child transmission, interventions, retention, uptake  
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29 **80 Strengths and Limitations of this review:**  
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- 31 81 • A comprehensive search was conducted, including grey literature sources and hand  
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33 82 searching.  
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35 83 • A broad range of intervention categories, as well as, both maternal and infant outcomes  
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37 84 from across the spectrum of the PMTCT cascade were included.  
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39 85 • Our search was limited to studies conducted in low- and middle-income countries in  
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41 86 order to increase utility of findings to LMIC PMTCT programmers  
42  
43 87 • The multifaceted nature of the interventions and variability in outcomes reported, limited  
44  
45 88 our ability to combine studies statistically.  
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47 89 • Due to the small number of studies included in the meta-analysis publication bias could  
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52 90 not be examined.  
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## 92 **Introduction:**

93 In 2015, 150,000 new HIV infections and 110,000 HIV-related deaths occurred globally among  
94 children <15 years of age, with mother to child transmission the leading cause of new HIV  
95 infections among children (1,2). Despite effectiveness of prevention of mother to child  
96 transmission (PMTCT) of HIV regimens (3,4), uptake of and retention in PMTCT care remains  
97 below target in many low and middle-income countries (LMICs) (4,5,6). While progress has  
98 been made in understanding barriers to uptake and retention of women and their infants in  
99 PMTCT services (7), evidence to provide guidance to LMIC implementers and policy makers  
100 seeking to optimize PMTCT services remains limited.

101  
102 Eight systematic reviews have been conducted on strategies to optimize PMTCT. Two of these  
103 reviews evaluated the effectiveness of interventions, specifically, male involvement (8) and  
104 integration of services (9), to improve coverage of PMTCT services. These reviews were limited  
105 by the lack of studies to provide recommendations. A third review (10) examined the effects of  
106 integration of antenatal care with postnatal and other health services for a broad range of  
107 maternal health outcomes in LMICs; although some PMTCT studies and outcomes were  
108 included, this was not the focus of the review. A fourth -systematic review evaluated  
109 interventions for improving initiation of antiretroviral therapy (ART) therapy in pregnant women  
110 (11) and found the evidence quality insufficient to support recommendations. A fifth systematic  
111 review (12) assessed the impact of China's PMTCT cascade in improving uptake and outcomes  
112 at various steps along the cascade; specific interventions implemented to operationalize the  
113 cascade were not reported. Three systematic reviews have been published since the initiation of  
114 the present review. One review evaluated non-pharmacological interventions to improve quality



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3 115 of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of  
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5 116 included studies reported PMTCT outcomes, this was not a primary focus of the review. A  
6  
7 117 second review focused on postpartum retention of women in PMTCT and ART care (14). This  
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9 118 review focused on a limited portion of the PMTCT cascade. A third review (15) focused on  
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11 119 interventions to improve PMTCT service delivery and promote retention. This review included a  
12  
13 120 range of study designs and studies conducted in both high and low-middle income countries and  
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15 121 as such, is of less value as a guide to decision making for PMTCT policy and programming in  
16  
17 122 LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by:  
18  
19 123 lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade  
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21 124 and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high  
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23 125 income country studies where the context of PMTCT care is often substantially different than in  
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25 126 LMICs.  
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33 128 This review was developed in collaboration with knowledge users from the Malawi Ministry of  
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35 129 Health's HIV treatment and care technical working group. The objective of this current review  
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37 130 was to identify what interventions at the patient, provider, or health system level are effective  
38  
39 131 compared to no intervention or usual care in improving uptake and retention of HIV-positive  
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41 132 mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health  
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43 133 services in LMICs, this review is targeted to provide guidance for PMTCT policy and  
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45 134 programming in LMICs, and therefore included a broad range of intervention categories, as well  
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47 135 as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.  
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3 **138 Methods:**  
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5 **139 Protocol:** A protocol was developed for this review based on the Cochrane Handbook for  
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8 **140** systematic reviews (16) and the Cochrane Effective Practice and Organisation of Care Group  
9  
10 **141** (EPOC) (17) and registered with PROSPERO (CRD42015020829, available at:  
11  
12 **142** [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015020829#](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020829#).  
13  
14 **143** VXHCNUZBn5I). The complete protocol was previously published and the methods are  
15  
16 **144** presented briefly here (18). Our findings are reported using the PRISMA statement for reporting  
17  
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19 **145** systematic reviews (19).  
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22 **146**  
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24 **147 Patient and Public Involvement:**  
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26 **148** No patients were involved in this study.  
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29 **149**

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31 **150 Eligibility Criteria:**  
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33 **151** We included studies reporting the effectiveness of interventions in improving uptake and/or  
34  
35 **152** retention of HIV-positive pregnant or breast feeding women and their children from birth to 2  
36  
37 **153** years of age or termination of breast feeding in PMTCT services. We included randomized,  
38  
39 **154** quasi-randomized and non-randomized controlled trials, and interrupted time series studies that  
40  
41 **155** compared usual care or no intervention to any type of intervention at the patient, provider, or  
42  
43 **156** health system level. Although included in error in the Prospero registration for our review,  
44  
45 **157** controlled before and after studies were not included in the protocol manuscript or search.  
46  
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48 **158** Studies were included if conducted in LMICs as defined by the EPOC filter (20) and updated  
49  
50 **159** using the most recent World Bank World Country and Lending group classification (21). Studies  
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52 **160** that included both high and low/middle- income countries were eligible for inclusion if LMICs  
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3 161 results could be abstracted. No restriction was placed based on language of publication,  
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5 162 publication status, study time frame, or duration of follow-up.  
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10 164 Information Sources and Literature Search:  
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12 165 A search strategy was developed in consultation with an experienced information specialist  
13  
14 166 (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review  
15  
16 167 of Electronic Search Strategies checklist (22). The following databases were searched from  
17  
18 168 inception to July 31, 2015 and subsequently updated using the same search strategy for the  
19  
20 169 period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV,  
21  
22 170 pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and  
23  
24 171 retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global  
25  
26 172 Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science,  
27  
28 173 Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE,  
29  
30 174 ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library,  
31  
32 175 WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov.  
33  
34 176 Several databases planned for inclusion in our search were no longer available or not accessible  
35  
36 177 by our group at the time of the search and were therefore not included: AIDS Education Global  
37  
38 178 Information System, British Library Catalogue, and the New York Academy of Grey Literature.  
39  
40 179 In addition, we searched reference lists of included articles, and contacted several experts in the  
41  
42 180 field to inquire about eligible unpublished or in progress studies. See supplementary file for  
43  
44 181 complete MEDLINE search strategy.  
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54 183 Study Selection and Data Collection Process:  
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3 184 A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a  
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5 185 sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement.  
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8 186 Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then  
9  
10 187 abstracts were screened, and second, the full-text articles were screened. Translation software  
11  
12 188 was utilized to screen articles at the titles and abstracts level, with no non-English articles  
13  
14  
15 189 remaining at the full article review phase. A data abstraction form was created using the EPOC  
16  
17 190 data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in  
18  
19 191 screening and data extraction. A calibration exercise was conducted with completed data  
20  
21  
22 192 extraction forms compared and discussed for each of the first 3 articles to ensure consistency;  
23  
24 193 data extraction was then completed for the remaining articles independently and in duplicate by 2  
25  
26 194 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each  
27  
28 195 study included: population, intervention, comparator, context, outcomes, study design, time  
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30  
31 196 frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes  
32  
33 197 were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment,  
34  
35 198 percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis,  
36  
37  
38 199 and percentage of women and infants retained in PMTCT care/completing the ART regimen as  
39  
40 200 defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of  
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42 201 infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants  
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44 202 completing post-exposure HIV testing 6 weeks following termination of breast feeding for all  
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47 203 infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV;  
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49 204 adverse events; major or minor congenital malformations; small for gestational age; pre-mature  
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51 205 delivery; still birth; and infant death within first 2 years of life (18).  
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3 207 When necessary to clarify published data or to obtain unpublished data, we contacted primary  
4  
5 208 authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions,  
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8 209 and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to  
9  
10 210 calculate risk ratios were not available in the publication. Three responded and provided the  
11  
12 211 requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional  
13  
14 212 data as they were submitting the manuscript for publication.  
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19 214 Methodological Quality/Risk of Bias Appraisal:

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21 215 Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the  
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23 216 Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies  
24  
25 217 included in the meta-analysis, risk of publication bias could not be examined using funnel plots.  
26  
27 218 Selective reporting bias was assessed through review of trial registrations where available and  
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29 219 categorized as unclear if not registered.  
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35 221 Data Synthesis:

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37 222 Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy  
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39 223 for health system interventions and discrepancies resolved through discussion (23). Clinical  
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41 224 heterogeneity was determined based on patient, intervention, and outcome characteristics.  
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43 225 Descriptive synthesis of study results were conducted for all studies, and are reported narratively  
44  
45 226 and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate  
46  
47 227 intervention effects using the Metafor Package in the statistical software R (24). Statistical  
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49 228 heterogeneity was examined using the  $I^2$  statistic, with  $I^2 \geq 75\%$  indicating significant  
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52 229 heterogeneity (16).  
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231 **Results:**232 Literature Search:

233 A total of 29,837 articles were identified through the database and hand search. After duplicates  
 234 were removed 21,354 titles and abstracts were screened and 95 articles reviewed in full. Thirty-  
 235 four articles representing 18 studies with 16 companion reports met eligibility criteria (Figure 1,  
 236 flow diagram).

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238 Study Characteristics:

239 Study characteristics are outlined in Table 1 (see supplementary file table for complete study  
 240 characteristics).

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242 Table 1: Characteristics of Included Studies

| Author(s); Year | Intervention Level/Type | Study Design                              | Country; Geographic Location in Country           | Study Population  | Intervention   | Comparison | Intervention Classification EPOC            | Number of Participants     | Participant Characteristics   | Outcomes   |
|-----------------|-------------------------|---|---|---|--|------------|---|----------------------------|---|--|
| Ezeanolue; 2015 | Patient                 | Mixed Methods Including Small Cluster RCT | Nigeria (Enugu state)                             | Self-identified pregnant women $\geq 18$ years who attended any church site | Monthly baby showers offered health education and onsite laboratory testing including HIV testing, and Mama Packs for essential items during pregnancy | Usual care | • Outreach services                         | 40 churches, 3002 patients | • % HIV positive: 2% overall<br>• Maternal age (mean): I = 29.3, C = 29.7 | 1) ART during pregnancy<br>2) Retention in care at 6-8 week postpartum |
| Reynolds; 2010  | Patient                 | Cluster RCT                               | Kenya (Coast, Rift Valley, and Western provinces) | HIV-positive pregnant women $\geq 18$ and at least 32 weeks gestation       | PMTCT providers trained to prepare and counsel women on how to store and   | Usual care | • Self-management<br>• Educational outreach | 10 Clusters: 160 patients  | • Maternal age (mean): I = 27.4, C = 28.4                                 | Infant ART prophylaxis at birth  |

|                |                  |             |  |  |  |  |  |                             |  |  |
|----------------|------------------|-------------|--|--|--|--|--|-----------------------------|--|--|
|                |                  |             |  |  | administer take-home nevirapine infant dose  |  |  |                             |  |  |
| Weiss; 2014    | Patient          | RCT         | South Africa (Gert Sibande and Nkangala districts) | HIV-positive pregnant women, 24 to 30 weeks gestation, and ≥18 years of age, recruited and asked to invite their male partner to enroll as a couple. | 4 successive weekly sessions employed a cognitive-behavioral approach and addressed HIV, safer sex, sexual negotiation, and PMTCT issues. Sessions were closed, structured, of gender-concordant groups, led by trained gender-matched facilitators, and conducted in ANCs.                          | Time-matched health education sessions | • Group (couple) vs individual care              | 12 Clusters<br>478 couples  | • % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive<br>• Maternal age (mean): I = 28.3; C = 28.1 | 1) ART detected in mother blood samples at birth<br>2) ART detected in infants blood at birth<br>3) Infant HIV-positive rate at 6 weeks            |
| Yotebing; 2016 | Patient          | RCT         | Democratic Republic of Congo (Kinshasa)            | Newly diagnosed HIV-positive women, ≤32 weeks gestation, registering for ANC   | Participants received small escalating cash payments, starting at US \$5 and increasing by \$1 each visit. If attended scheduled clinic appointments and completed recommended actions. Incentive reset to its original value if mother failed to complete any actions required at a specific visit. | Usual care                             | • Conditional cash transfer                      | 433 women                   | • Maternal age (median): I = 29.5, C = 29.0  | 1) Retention in care at 6 weeks postpartum<br>2) Uptake of PMTCT services through to 6 weeks postpartum<br>3) Infant HIV-positive rates at 6 weeks |
| Richter, 2014  | Patient/Provider | Cluster RCT | South Africa (KwaZulu-Natal)                       | HIV-positive women, ≥18 years of age and <34 weeks   | 8-session intervention conducted by peer mentors (4 antenatal,   | Usual care                             | • Role expansion or task shifting<br>• Education | 8 Clusters<br>1200 patients | • Maternal age (mean):(I = 26.5; C = 26.5  | 1) ART from the 28th week of pregnancy (AZT  |

|                       |                 |                        |                     |   |  |            |   |                             |  |  |
|-----------------------|-----------------|------------------------|---------------------|---|--|------------|---|-----------------------------|--|--|
|                       |                 |                        |                     | pregnant  | 4 postnatal) to support HIV-positive women through pregnancy and early motherhood. HIV-positive women recruited, trained and certified as peer mentors prior to implementation; in-person supervision was provided weekly.                               |            | al meetings   |                             |  | or HAART )<br>2) ART during labor (AZT or HAART<br>3) NVP or HAART during labor<br>4) Infant NVP at birth<br>5) AZT dispensed for infant and medicated as prescribed |
| Kieffer; 2011         | Provider        | Cluster RCT            | Swaziland           | All pregnant women presenting for delivery at participating maternity facilities        | 1-day training course provided to nurse-midwives to increase knowledge and skills in provision of PMTCT and to enhance confidence and counseling skills.   | Usual care | • Educational meetings  | 6 Clusters<br>2444 Patients | % HIV positive at enrollment: 33% overall  | NVP in cord blood  |
| Dryden-Petersen; 2015 | Provider/System | Step wedge Cluster RCT | Botswana (Gaborone) | ART-naïve, HIV-positive women registering at antenatal clinic before 26 weeks gestation | 2-hour clinical staff education sessions on protocols for CD4 testing; open-source platform permitting automated SMS to monitor/deliver CD4 results between central labs and clinics; longitudinal support for tracing women eligible for ART initiation | Usual care | • The use of information and communication technology<br>• Educational meetings | 19 Clusters<br>336 women    | % HIV positive: I = 189 (47.6%) and C = 177 (44.6%)<br>• Maternal age (median): (I = 28; C = 29) | ART initiation by 30 wks gestation   |



|                       |                     |                              |   |  |   |   |   |  |   |  |
|-----------------------|---------------------|------------------------------|---|--|---|---|---|--|---|--|
| Mwapa<br>sa;<br>2017  | Provider/Sy<br>stem | 3<br>Arm,<br>Cluste<br>r RCT | Malawi<br>(Salima<br>and<br>Mangoch<br>i<br>districts)    | HIV-<br>positive<br>pregnant<br>women<br>initiated<br>on<br>Option<br>B+<br>regimen  | MIP-<br>integration<br>of<br>HIV/ANC,<br>routine<br>tracing<br><br>MIP +<br>SMS,<br>integrated<br>HIV/ANC<br>care, SMS<br>sent to<br>community<br>health<br>worker to<br>trace if<br>appointme<br>nt missed | Usual<br>care:<br>non-<br>integrate<br>d care,<br>routine<br>tracing<br>as for<br>MIP | •<br>Integration<br>• The use<br>of<br>informatio<br>n and<br>communic<br>ation<br>technology | 30<br>Clusters<br>1350<br>women  | • Maternal<br>age<br>(median):<br>MIP = 29.5;<br>MIP+SMS<br>= 29.2;<br>SOC = 29.4 | 1)<br>Materna<br>l<br>retentio<br>n in<br>care at<br>12<br>months<br>postpart<br>um trial<br>data<br>2) Infant<br>retentio<br>n in<br>care at<br>12<br>months<br>postpart<br>um trial<br>data<br>3)<br>Materna<br>l<br>retentio<br>n in<br>care at<br>12<br>months<br>using<br>MOH<br>definitio<br>n<br>4) Infant<br>retentio<br>n in<br>care at<br>12<br>months<br>using<br>MOH<br>definitio<br>n |
| Oyeled<br>un;<br>2017 | Provider/Sy<br>stem | Cluste<br>r RCT              | Northern<br>Nigeria<br>(Benue<br>and<br>Kaduna<br>states) | HIV-<br>positive,<br>women,<br>gestation<br>al age <=<br>34<br>weeks,<br>who were<br>ART<br>naive and<br>agreed to<br>start<br>lifelong<br>ART | QI teams<br>established<br>, visits by<br>coaches<br>and<br>collaborativ<br>e meetings  | Routine<br>MOH<br>support   | •<br>Continuou<br>s quality<br>improvem<br>ent  | 32<br>Clusters:<br>(6 later<br>excluded<br>)<br>532<br>women<br>(21<br>withdrew<br>leaving<br>511 in<br>total) | • Maternal<br>age<br>(median): I<br>= 27 ; C =<br>27                              | 1) ART<br>initiated<br>within 2<br>week of<br>enrolme<br>nt<br>2)<br>Retenti<br>on in<br>care at<br>6<br>months<br>3)<br>Infants<br>starting<br>prophyl<br>axis<br>within<br>72<br>hours<br>4) infant<br>HIV<br>testing<br>at 6-10<br>weeks  |
| Phiri;<br>2017        | Provider/Sy<br>stem | 3<br>Arm,<br>Cluste<br>r RCT | Malawi<br>(SE, SW<br>and<br>Central<br>West               | Pregnant<br>and<br>breastfee   | FBPS -<br>women<br>received<br>SOC and<br>met with  | SOC =<br>standard<br>of care<br>facilities<br>provided                                | • Role<br>expansion<br>or task<br>shifting<br>outreach  | 21<br>Clusters<br>1269<br>women  | • Maternal<br>age<br>(median<br>across all 3                                      | 1) ART<br>uptake<br>2)<br>Retaine<br>d in  |

|  |  |  |        |   |  |  |   |  |           |   |
|--|--|--|--------|---|--|--|---|--|-----------|---|
|  |  |  | Zones) | ding HIV-positive women and their infants. Up to 3 male sex partners could be enrolled per patient. | “mentor mothers”, HIV-positive women who had recently completed PMTCT and were on ART. Mentor mothers provided 1-on-1 support at each clinic visit, led weekly clinic-based support groups, and contacted women within 1 week of a missed appointment. CBPS-women received SOC and met with “expert mothers”, HIV-positive women who recently completed PMTCT and were on ART. Expert mothers conducted routine home visits to provide HIV education and clinic visit reminders, and led monthly community-based support group meetings. Expert mothers were responsible for contacting women in the community | routine HIV care according to Malawi MOH guidelines. According to national guidelines, women who fail to attend the clinic within 60 days of a missed appointment are supposed to be traced. However, this rarely occurs in the routine program. | services<br>• The use of information and communication technology |  | arms): 27 | care at 1 year:<br>3) Retained in care at 2 years trial data<br>4) Retained in care at 2 years MOH definition<br>5) Infant HIV tested at 6 weeks<br>6) Infant HIV-positive at 6 weeks |
|--|--|--|--------|---|--|--|---|--|-----------|---|

|                        |                     |                 |   |  |  |   |  |                                   |  |   |
|------------------------|---------------------|-----------------|---|--|--|---|--|-----------------------------------|--|---|
|                        |                     |                 |   |  | within 1 week of a missed clinic visit.  |   |  |                                   |  |   |
| Tomlins<br>on;<br>2014 | Provider/Sy<br>stem | Cluste<br>r RCT | South<br>Africa<br>(Umlazi)                               | Pregnant<br>women<br>aged ≥17<br>and their<br>newborns<br>residing<br>in the<br>clusters<br>during<br>the<br>recruitme<br>nt period  | CHWs<br>were<br>trained to<br>carry out<br>structured<br>home visits<br>using<br>motivationa<br>l<br>interviewin<br>g for<br>breastfeedi<br>ng<br>counseling.<br>Women<br>were<br>scheduled<br>to receive<br>7 home-<br>based<br>visits<br>during<br>pregnancy<br>and post-<br>delivery.<br>Low birth<br>weight<br>neonates<br>received 2<br>extra visits<br>within the<br>first week  | In control<br>clusters,<br>CHWs<br>provided<br>informati<br>on and<br>support<br>on<br>accessin<br>g social<br>welfare<br>grants<br>and<br>conducte<br>d three<br>home-<br>based<br>visits:<br>during<br>pregnanc<br>y and<br>post-<br>delivery.                | • Role<br>expansion<br>or task<br>shifting<br>• Outreach<br>services             | 30<br>Clusters<br>3957<br>women   | Maternal<br>age<br>(median): I<br>= 23; C =<br>23    | 1) Infant<br>HIV<br>testing<br>by 6<br>weeks<br>2)<br>Infant<br>HIV-<br>positive<br>at 12<br>weeks  |
| Aliyu;<br>2016         | System              | Cluste<br>r RCT | Rural<br>north-<br>central<br>Nigeria<br>(Niger<br>State) | HIV-<br>positive<br>women<br>and their<br>infants,<br>presentin<br>g for ANC<br>or<br>delivery<br>who met<br>1 of<br>following<br>criteria:<br>unknown<br>HIV<br>status at<br>presentati<br>on;<br>history of<br>ART<br>prophylax<br>is or<br>treatment<br>, but not<br>receiving<br>ARTs at<br>presentati<br>on; or<br>known<br>HIV<br>status but<br>had never<br>received<br>treatment | Integrated<br>package of<br>PMTCT<br>services<br>that<br>included<br>point-of-<br>care CD4<br>cell count<br>or<br>percentage<br>testing,<br>transition<br>of<br>decentraliz<br>ed PMTCT<br>tasks to<br>trained<br>midwives,<br>integrated<br>mother and<br>infant care<br>services,<br>active<br>influential<br>family<br>member<br>(male<br>partner)<br>participati<br>on, and<br>community<br>involvemen<br>t (male<br>community<br>peer<br>champions<br>providing | Standard<br>of care<br>included<br>health<br>informati<br>on, opt-<br>out HIV<br>testing,<br>infant<br>feeding<br>counselin<br>g,<br>referral<br>for CD4<br>cell<br>counts<br>and<br>treatment<br>, ART<br>prophyla<br>xis, and<br>early<br>infant<br>diagnosis | • Role<br>expansion/<br>task<br>shifting<br>Integration<br>• Packages<br>of care | 12<br>Clusters<br>369<br>patients | • Maternal<br>age<br>(median): I<br>= 26 ; C =<br>28 | 1)<br>Materna<br>l ART<br>initiation<br>2)<br>Materna<br>l-infant<br>retentio<br>n in<br>care at<br>6 week<br>postpart<br>um<br>3)<br>Materna<br>l-infant<br>retentio<br>n in<br>care at<br>12<br>weeks<br>post<br>partum |

|                       |        |                        |                            |   |   |            |  |   |  |  |
|-----------------------|--------|------------------------|----------------------------|---|---|------------|--|---|--|--|
|                       |        |                        |                            |   | outreach, education, and linkage of male partners to key referral services)   |            |  |   |  |  |
| Geelhoed; 2013        | System | Cluster RCT            | Mozambique (Tete province) | Public primary health facilities providing maternal child health and PMTCT services Mothers and their children up to 5 years of age.                      | Reorganized services to deliver integrated consultations and services for mothers and their children up to 5 years of age.  | Usual care | <ul style="list-style-type: none"> <li>Integration</li> <li>Educational meetings</li> </ul>                  | 6 Clusters  | Not available  | 1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 3) Infant HIV-positive |
| Killam; 2010          | System | Step wedge Cluster RCT | Zambia (Lusaka)            | ART eligible pregnant women presenting at participating clinics   | Integration of ART care into ANC. Women already receiving ART at the general ART clinic encouraged to continue receiving their services in the general ART clinic     | Usual care | <ul style="list-style-type: none"> <li>Integration</li> </ul>  | 8 Clusters 31536 patients                           | <ul style="list-style-type: none"> <li>% HIV positive: I = 21.8%; C = 22.2%</li> <li>Maternal age (mean): I = 27.5; C = 27.3</li> </ul>  | ART initiation during pregnancy  |
| Odeny; 2014           | System | RCT                    | Kenya (Nyanza region)      | HIV-positive women attending antenatal or HIV care; >=18 years of age; between 28 weeks gestation and delivery; enrolled in PMTCT; access to mobile phone | Custom-built, automated software to send and receive text messages. Sent 14 text messages, up to 8 sent during pregnancy, and weekly for first 6 weeks after delivery | Usual care | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul>        | 388 Patients  | <ul style="list-style-type: none"> <li>% HIV positive: 29.3% (388/1324)</li> <li>Maternal age (mean): (I = 30.8% 18-24, 56.9% 25-34, 12.3% 35+; C = 33.7% 18-24, 57.5% 25-34, 8.8% 35+)</li> </ul> | 1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks     |
| Rotherham-Borus; 2014 | System | Cluster RCT            | South Africa (Cape Town)   | Pregnant women >= 18 years of age from Cape Town townships  | Antenatal and postnatal home visits by CHW in addition to standard clinic-based care  | Usual care | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Outreach services</li> </ul> | 26 Clusters: (2 later removed); 1144 eligible women | <ul style="list-style-type: none"> <li>%HIV positive: I = 149 (25.5%); C = 146 (26.7%)</li> <li>Mean maternal age: I = 26.5; C = 26.3</li> </ul>   | 1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART                       |

|               |        |             |                                  |   |   |   |                                  |                              |  |  |
|---------------|--------|-------------|----------------------------------|---|---|---|----------------------------------|------------------------------|--|--|
|               |        |             |                                  |   |   |   |                                  |                              |  | at onset of labor<br>4) Infant prophylaxis within 24 hours of birth<br>5) AZT dispensed for infant and medicated as prescribed<br>6) Infant HIV test at 6 weeks  |
| Rustagi; 2016 | System | Cluster RCT | Cote d'Ivoire, Kenya, Mozambique | Public and non-profit health facilities with PMTCT services. Pregnant women presenting for antenatal care | A five-step, facility-level systems analysis and improvement intervention designed to maximize effectiveness of PMTCT service delivery by improving understanding of inefficiencies   | Usual care  | • Continuous quality improvement | 36 Clusters<br>1876 patients | Not available  | 1) ART in pregnancy<br>2) Infants HIV tested by 6-8 weeks  |
| Turan; 2015   | System | Cluster RCT | Kenya (Nyanza Province)          | Pregnant HIV-positive women $\geq 18$ , not enrolled in HIV care at baseline and their infants            | Integrated clinics provided PMTCT and HIV care and treatment services within existing ANC services, starting prenatally and continuing until a definitive pediatric HIV diagnosis was obtained or the child reached 18 months of age. | Non-integrated ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women to a separate HIV clinic at the same facility | • Integration                    | 12 Clusters:<br>1172 women   | • %HIV positive: I = 48.5%, C = 51.5%<br>• Maternal age (mean): I = 25.0, C = 24.8 | 1) ART during pregnancy<br>2) ART during Labor<br>3) ART after birth<br>4) Infant ART after birth<br>5) ART use throughout all 3 PMTCT periods<br>6) Infant HIV testing by 3 months<br>7) Infant HIV testing at 9 months |

|  |  |  |  |  |  |  |  |  |  |   |
|--|--|--|--|--|--|--|--|--|--|---|
|  |  |  |  |  |  |  |  |  |  | 8)<br>Infants<br>HIV<br>tested<br>by 6<br>weeks<br>9)<br>Infants<br>HIV-<br>positive<br>at 6<br>weeks<br>10)<br>Infants<br>HIV<br>tested<br>by end<br>of study<br>(up to<br>12<br>months)<br>11)<br>Infants<br>HIV-<br>positive<br>at 9<br>months |
|--|--|--|--|--|--|--|--|--|--|---|

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245 The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge  
 246 design, and 2 RCTs. The number of clusters ranged from 6 to 40, and participants across all  
 247 study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan  
 248 Africa between 2005 and 2016. Half of included studies reported multifaceted interventions  
 249 including 2 or more EPOC category components [9/18] and as a result several were categorized  
 250 at more than 1 intervention level: patient [4], provider [1], system [7], patient/provider [1], or  
 251 provider/system [5]. Interventions directed all or in part to the health system level were most  
 252 common [12/18]. Integration [5/18], role expansion or task shifting [5/18], outreach services  
 253 [4/18], and use of information and communication technology [4/18] were the most common  
 254 EPOC intervention categories employed alone or as part of a complex intervention.

255

256 Reporting of population characteristics varied widely across studies as did outcome definitions.

257 Seven studies limited participation to pregnant women 17-18 years of age or older; median ages

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2  
3 258 across the studies ranged from 23 to 29.7 years. Marital status was reported in 14 studies, and  
4  
5 259 varied widely from 9% to 99% of women who were married or had a live-in partner. Maternal  
6  
7 260 education level was reported in 12 studies; 5 studies reported the majority of women having no  
8  
9  
10 261 or primary education, 5 studies reported the majority of women having received secondary  
11  
12 262 education, and, 2 reported mean/median years of education [10.3 years, 10 years [range 8-  
13  
14 263 12years]]. Maternal employment [6/18] and parity [2/18] status were reported in a minority of  
15  
16  
17 264 studies (Table 1). No pre-specified adverse events were reported in the identified studies.  
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20 265

21 266 Reported outcomes varied substantially across studies, with few studies within intervention  
22  
23 267 categories reporting comparable outcomes. For example, 5 studies reported interventions  
24  
25 268 employing integration alone [2] or in combination with other interventions [3], with only 1  
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27  
28 269 PMTCT outcome in common among the 2 studies employing integration alone. The most  
29  
30 270 commonly reported outcomes were maternal ART use during pregnancy and labor and delivery,  
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33 271 infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.  
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37  
38 273 As a result of the multifaceted nature of the majority of interventions employed, and variability  
39  
40 274 in PMTCT outcomes reported, the ability to combine results statistically was limited.  
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#### 44 276 Methodological Quality:

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47 277 Risk of bias was assessed using the Cochrane EPOC risk of bias criteria (17). Five of the 18  
48  
49 278 studies were appraised as low risk of bias on 3 or more (4 with 3, 1 with 4) of the 6 main criteria.  
50  
51 279 The most common issues encountered were unclear reporting of randomization (8/18) and  
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53  
54 280 allocation concealment (11/18), and unclear reporting or high risk of bias due to lack of blinding  
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281 of participants/personnel (18/18) and blinding of outcome assessment (16/18) (The complete risk  
282 of bias table is included as an additional file).

283

284 Meta-analysis of Effect of Integration of care on ART use during pregnancy:

285 We expected variation in the implementation of integrated care of ART therapy into ANC in the  
286 two studies, conducted in clinics in Zambia and Kenya. We also expected some variation in  
287 standard care in the two settings, particularly with respect to eligibility and timing of ART  
288 initiation across the two studies both of which experienced policy changes during the course of  
289 the study. We therefore used a random-effects meta-analysis to derive the combined effect  
290 estimate of integrated care based on theoretical grounds although the  $I^2$  was not significant.

291 Two studies assessing integration of HIV and antenatal care relative to usual non-integrated care  
292 were combined in a meta-analysis of 1,887 patients (25,26); there was increased use of ARTs  
293 during pregnancy with integration of HIV and antenatal care compared to standard non-  
294 integrated care, non-integrated care, (AOR=2.69; 95% CI=1.25, 5.78; P=0.0113,  $I^2=59.26\%$ )  
295 (Figure 2) (see supplementary file for fixed effects meta-analysis diagram) .

296

297 Descriptive Synthesis:

298 Details of included studies (country, intervention, population characteristics, outcomes, etc.) and  
299 outcomes are outlined in Table 1 and 2.

300

301 Table 2: Results of Included Studies

| Author: Year    | Intervention Level/Type | Intervention Classification EPOC | Intervention         | Control    | Outcomes Intervention Group          | Outcomes Control Group               | Risk Ratio (95%CI)    | Adjusted Statistic where provided |
|-----------------|-------------------------|----------------------------------|----------------------|------------|--------------------------------------|--------------------------------------|-----------------------|-----------------------------------|
| Ezeanolue; 2015 | Patient                 | • Outreach                       | Monthly baby showers | Usual care | 1) ART during pregnancy: 24/41 (65%) | 1) ART during pregnancy: 12/32 (50%) | 1) 1.56 (0.93 - 2.62) | 1) AOR 2.8 (1.02-4.79)            |



|                       |                  |   |   |   |  |   |   |  |
|-----------------------|------------------|---|---|---|--|---|---|--|
|                       |                  | services  |   |   | 2) Retention in care at 6-8 week postpartum: 33/41(81%)  | 2) Retention in care at 6-8 week postpartum: 28/32(88%)   | 2) 0.92 (0.75-1.12)   | 2) AOR 0.39 (0.04-3.99)  |
| Reynolds; 2010        | Patient          | <ul style="list-style-type: none"> <li>Self-management</li> <li>Educational outreach</li> </ul>                 | Take home infant nevirapine dose  | Usual care                              | Infant ART prophylaxis at birth: 80/85 (94%)   | Infant ART prophylaxis at birth: 66/75 (88%)  | 1.07 (0.97-1.18)  | --   |
| Weiss; 2014           | Patient          | <ul style="list-style-type: none"> <li>Group (couple) vs. individual care</li> </ul>                            | Couples HIV risk reduction and PMTCT education sessions                         | Time matched general education sessions | 1) ART detected in mother blood samples at birth: 9/12 (75%)<br>2) ART detected in infants blood at birth: 12/13 (92%)<br>3) Infant HIV positive at 6 weeks: 1/30 (3.3%)   | 1) ART detected in mother blood samples at birth: 16/12 (50%)<br>2) ART detected in infants blood at birth: 9/12 (75%)<br>3) Infant HIV positive: 3/39 (7.7%)   | 1) 1.50 (0.78-2.88)<br>2) 1.23 (0.86-1.77)<br>3) 0.43 (0.05-3.96)   | --   |
| Yotebieng; 2016       | Patient          | <ul style="list-style-type: none"> <li>Conditional cash transfer</li> </ul>                                     | Cash payments for clinic attendance and acceptance of recommended services      | Usual Care                              | 1) Retention in care at 6 weeks postpartum: 174/216 (80.6%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 146/216 (67.6%)<br>3) HIV positive infants at 6 weeks: 5/169 (3.0%)  | 1) Retention in care at 6 weeks postpartum: 157/217 (72.4%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%)<br>3) HIV positive infants at 6 weeks: 6/156 (3.9%)   | 1) 1.11(1.00-1.23)<br>2) 1.26(1.08-1.48)<br>3) 0.77(0.24-2.47)  | 1) ARD 1.13 (1.02-1.26)<br>2) ARD 1.31 (1.12-1.54)<br>3) –   |
| Richter, 2014         | Patient/Provider | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Educational meetings</li> </ul> | Peer Mentor led educational meetings  | Usual Care                              | 1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%)<br>2) ART during labor (AZT or HAART): 282/377 (74.8%);<br>3) NVP or HAART during labor: 361/377 (95.8%)<br>4) Infant NVP at birth: 364/377 (96.6%)<br>5) AZT dispensed for infant and medicated as prescribed: 348/377 (92.3%) | 1) ART from the 28th week of pregnancy (AZT or HAART): 455/466 (95.5%)<br>2) ART during labor (AZT or HAART): 334/466 (71.7%)<br>3) NVP or HAART during labor: 456/466 (97.9%)<br>4) Infant NVP at birth: 451/466 (96.8%)<br>5) AZT dispensed for infant and medicated as prescribed: 374/466 | 1) 0.92 (0.89-0.96)<br>2) 1.04 (0.96-1.13)<br>3) 0.98 (0.95-1.00)<br>4) 1.00 (0.97-1.02)<br>5) 1.15 (1.09-1.21) | 1) AOR 0.44 (0.26,0.74)<br>2) AOR 1.16(0.44, 3.02)<br>3) AOR 0.53 (0.20, 1.41)<br>4) AOR 1.00 (0.36, 2.79)<br>5) AOR 2.98 (0.78,11.30) |
| Kieffer; 2011         | Provider         | <ul style="list-style-type: none"> <li>Educational meetings</li> </ul>  | 1 day PMTCT training for nurses and midwives                                    | No additional training                  | NVP in cord blood: 373/465(80%)  | NVP in cord blood: 325/472 (69%)  | 1.17 (1.08, 1.26)   | ---  |
| Dryden-Peterson; 2015 | Provider/System  | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul>           | Staff training in point of care CD4 testing and automated SMS results reporting | Usual care                              | ART initiated by 30 wks gestation: 56/154 (36.4%)  | ART initiated by 30 wks gestation: 37/153 (24.2%)   | 1.50 (1.06-2.13)  | AOR 1.06 (0.53,2.13)   |

|                |                  |  |  |   |  |   |   |  |
|----------------|------------------|--|--|---|--|---|---|--|
|                |                  | • Educational meetings   | to staff, support for patient tracing  |   |  |   |   |  |
| Mwapa sa; 2017 | Provider/Sy stem | • Integration of information and communication technology  | MIP= integration of antenatal and HIV care, routine patient tracing<br>MIP+SMS , integrated care and use of SMS enhanced tracing | Usual non-integrated care and patient tracing | 1) Maternal retention in care at 12 months postpartum trial data: MIP 89/461, 19.3%<br>MIP+SMS 115/493<br>2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3%<br>MIP+SMS 82/399, 20.1%<br>3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4%<br>MIP+SMS 332/493, 67%.<br>4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4%<br>MIP+SMS 323/399, 80.9% | 1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7%<br>2) Infant retention in care at 12 months postpartum trial data: SOC 32/300, 10.7<br>3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1%<br>4) Infant retention in care at 12 months using MOH definition: SOC 234/300, 78.0% | 1) MIP vs SOC 0.85 (0.65-1.10), MIP+SMS vs SOC 1.03 (0.81-1.31)<br>2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82)<br>3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06)<br>4) MIP vs SOC 0.97 (0.89-1.05), MIP+SMS vs SOC 1.04(0.96-1.12) | 1) MIP vs SOC ARR 0.85 (0.56-1.30), MIP+SMS vs SOC ARR 1.08 (0.87-1.35)<br>2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31)<br>3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05)<br>4) MIP vs SOC ARR 0.98 (0.89-1.09), MIP+SMS vs SOC ARR 1.01 (0.96-1.07) |
| Oyeledun; 2017 | Provider/Sy stem | • Continuous quality improvement   | QI teams established, coaching, and collaborative meetings   | Routine MOH support                           | 1) ART initiated within 2 week of enrolment: 233/247 = 94.3%<br>2) Retention in care at 6 months. 102/247 = 41.3%<br>3) Infants starting prophylaxis within 72 hours : 138/209 = 66%<br>4) Infant HIV testing at 6-10 weeks 102/209 = 48.8%;   | 1) ART initiated within 2 week of enrolment: 233/247 = 94.3%<br>2) Retention in care at 6 months. 102/247 = 41.3%<br>3) Infants starting prophylaxis within 72 hours 145/194 = 74.7%<br>4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%   | 1) 1.05 (1.01-1.08)<br>2) 1.07 (0.88-1.31)<br>3) 0.88 (0.78-1.00)<br>4) 1.93 (1.46-2.55)  | 1) --<br>2) ARR 1.08(0.78, 1.49)<br>3) ARR 0.95 (0.84, 1.07)<br>4) ARR 1.76(1.27, 2.42)  |
| Phiri; 2017    | Provider/Sy stem | • Role expansion or task shifting outreach services<br>• The use of information and communication technology | FBPS – facility based peer support from mentor mothers<br>CBPS- community based peer support from                                | SOC-standar d of care                         | 1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%)<br>2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%)<br>3) Retained in care at 2 years (trial data): FBPS- 223/428(52%)<br>CBPS- 211/394  | 1) ART uptake: SOC- 361/447(81%)<br>2) Retained in care at 1 year: SOC- 261/361 (74%)<br>3) Retained in care at 2 years (trial data): SOC- 169/447 (38%)  | 1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06-1.18)<br>2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10)<br>3) SOC vs FBPS 1.38(1.19-   | 1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18)<br>2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20)<br>3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30)<br>4) --  |

|                 |                 |  |  |   |  |  |   |  |
|-----------------|-----------------|--|--|---|--|--|---|--|
|                 |                 |  | mentor mothers   |   | (54%)<br>4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%)<br>5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%)<br>6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%) | 4) Retained in care at 2 years (MOH definition): SOC- 255/447(57%)<br><br>5) Infant HIV test at 6 weeks: SOC- 169/273(62%)<br><br>6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)                          | 1.60), SOC vs CBPS 1.42 (1.22-1.65)<br>4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43)<br>5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38)<br>6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09) | 5) --<br><br>6) ---  |
| Tomlinson; 2014 | Provider/System | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Outreach services</li> </ul>                     | 10 structured home visits from community health workers providing support in accessing social welfare grants | 3 home visits from community health workers | 1) Infant HIV testing by 6 weeks: 420/571(73.6%)<br>2) Infant HIV positive at 12 weeks: 28/568 (4.9%)  | 1) Infant HIV testing by 6 weeks: 465/698(66.6%)<br>2) Infant HIV positive at 12 weeks: 32/697 (4.6%)  | 1) 1.10 (1.03-1.19)<br>2) 1.07 (0.65-1.76)  | 1) ARR 1.10 (0.97, 1.25)<br>2) ARR 1.07 (0.69,1.66)                    |
| Aliyu; 2016     | System          | <ul style="list-style-type: none"> <li>• Role expansion /task shifting</li> <li>• Integration</li> <li>• Packages of care</li> </ul> | Integrated package of PMTCT services, family/male partner participation, community champions                 | Usual Care                                  | 1) Maternal ART initiation for PMTCT:166/172 (97%) 2) Maternal-infant retention in care at 6 weeks postpartum: 125/150 pairs (83%)<br>3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)                                      | 1) Maternal ART initiation for PMTCT: 77/197 (39%),<br>2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%)<br>3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%) | 1) 2.47 (2.07-2.95)<br>2) 9.44 (5.60-15.40)<br>3) 11.40 (6.40-20.34)  | 1) ARR 3.3 (1.4-7.8)<br>2) ARR 9.1 (5.2-15.9)<br>3) ARR 10.3(5.4-19.7) |
| Geelhoed; 2013  | System          | <ul style="list-style-type: none"> <li>• Integration</li> <li>• Educational meetings</li> </ul>                                      | Integrated maternal health and HIV care  | Usual Non-integrated care                   | 1) ART in labor: post intervention:112/121 (93%)<br>2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%);<br>3) Infants HIV-positive: post intervention: 9/123 (7%)  | 1) ART in labor: intervention phase =93/96(97%)<br>2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%)<br>3) Infants HIV positive: intervention phase: 7/60(12%)               | 1) 0.96 (0.90-1.02)<br>2) 0.93 (0.88-0.97)<br>3) 0.63 (0.25-1.60)   | --<br>--<br>--   |
| Killam; 2010    | System          | <ul style="list-style-type: none"> <li>• Integration</li> </ul>  | Integration of antenatal   | Usual non-integrated                        | ART initiation during pregnancy: 278/846 (32.9%)   | ART initiation during pregnancy:   | 2.28 (1.86-2.80)  | AOR 2.01 (1.37, 2.95)  |

|                      |        |  |   |                            |  |  |   |  |
|----------------------|--------|--|---|----------------------------|--|--|---|--|
|                      |        |  | and HIV care  | ed care                    |  | 103/716 (14.4%)  |   |  |
| Odeny; 2014          | System | • The use of information and communication technology    | SMS test messages during pregnancy and after delivery             | Usual care                 | 1) Maternal postpartum clinic attendance: 38/194 (19.6%)<br>2) Infant HIV testing by 8 wks: 1172/187 (92.0%)   | 1) Maternal postpartum clinic attendance: 22/187 (11.8%)<br>2) Infant HIV testing by 8 wks: 154/181 (85.1%)  | 1) 1.66 (1.03-2.70)<br>2) 1.08 (1.00-1.16)  | --<br>-  |
| Rotheram-Borus; 2014 | System | • Role expansion or task shifting<br>• Outreach services | Antenatal and postnatal home visits from community health workers | Usual care                 | 1) ART prior to labor: 169/179 (94.4%)<br>2) AZT or HAART during labor: 1164/179 (91.6%)<br>3) NVP or HAART at onset of labor: 166/179 (92.7%)<br>4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%)<br>5) Infant ART after birth: 172/179 (96.1%)<br>6) Infant HIV testing at 6 weeks: 155/160 (96.9%)   | 1) ART prior to labor: 149/159 (93.7%)<br>2) AZT or HAART during labor: 147/159 (92.5%)<br>3) NVP or HAART at onset of labor: 142/159 (89.3%)<br>4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%)<br>5) Infant ART after birth: 142/159 (89.3%)<br>6) Infant HIV testing at 6 weeks: 132/140 (94.3%)  | 1) 1.01 (0.95-1.06)<br>2) 0.99 (0.93-1.06)<br>3) 1.04 (0.97-1.11)<br>4) 1.08 (1.01-1.15)<br>5) 1.08 (1.01-1.14)<br>6) 1.03 (0.98-1.08)  | 1) AOR 1.08 (0.42, 2.80)<br>2) AOR 0.87 (0.39, 1.95)<br>3) AOR 1.52(0.70, 3.31)<br>4) AOR 2.94(1.41, 6.12)<br>5) AOR 2.95 (1.12, 7.73)<br>6) AOR 1.80 (0.62, 5.28)   |
| Rustagi; 2016        | System | • Continuous quality improvement                         | Facility level systems analysis and improvement intervention      | No-intervention            | 1) ART in pregnancy: 575/839 (69%)<br>2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)   | 1) ART in pregnancy: 664/1037(64%)<br>2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)   | 1) 1.07 (1.00-1.14)<br>2) 1.23 (1.09-1.40)  | --<br>--   |
| Turan; 2015          | System | • Integration  | Integrated HIV and antenatal care                                 | Usual, non-integrated care | 1) ART during pregnancy: 138/173 (80%)<br>2) ART during Labor: 28/173 (16%)<br>3) ART after birth: 22/173 (13%)<br>4) Infant ART after birth: 50/173 (29%)<br>5) ART throughout all 3 PMTCT periods: 37/176 (21.0%)<br>6) Infant HIV testing before 3 months: 143/569 (25%)<br>7) Infant HIV testing at 9 months: 361/569 (63%)<br>8) Infants HIV tested by 6 weeks: 143/568 (25%)<br>9) Infants HIV positive at 6 | 1) ART during pregnancy: 75/152 (49%)<br>2) ART during Labor: 84/152 (55%)<br>3) ART after birth: 57/152 (38%)<br>4) Infant ART after birth: 106/152 (70%)<br>5) ART throughout all 3 PMTCT periods: 23/153 (15.0%)<br>6) Infant HIV testing before 3 months: 106/603 (18%)<br>7) Infant HIV testing at 9 months: 326/603 (54%)<br>8) Infants HIV tested by 6 weeks: 106/594 (18%)<br>9) Infants HIV positive at 6 | 1) 1.61 (1.35-1.93)<br>2) 0.29 (0.20-0.42)<br>3) 0.34 (0.22-0.53)<br>4) 0.41 (0.32-0.54)<br>5) 1.40 (0.87-2.24)<br>6) 1.43 (1.14-1.79)<br>7) 1.17 (1.07-1.29)<br>8) 1.41 (1.13-1.76)<br>9) 0.64 (0.22-1.84) | 1) AOR 4.05 (2.0, 8.0)<br>2) AOR 0.16 (0.04, 0.68)<br>3) AOR 0.24 (0.08, 0.70)<br>4) AOR 0.18 (0.09, 0.35)<br>5) AOR 1.72 (0.85, 3.48)<br>6) AOR 1.57 (0.61,4.07)<br>7) AOR 1.47 (0.76,2.86)<br>8) AOR 1.57 (0.61-4.07)<br>9) AOR 0.62 (0.20,1.98)<br>10) AOR 1.45 (0.71,2.82) |

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|--|--|--|--|---|--|--|-----------------------------|
|  |  |  |  | weeks: 16/143<br>(4.2%)<br>10) Infants HIV<br>tested by end of<br>study (up to 12<br>m): 382/568<br>(67.3%)<br>11) Infants HIV<br>positive at 9<br>months: 28/382<br>(7.3%) | weeks: 7/106<br>(6.6%)<br>10) Infants HIV<br>tested by end of<br>study (up to 12<br>m): 338/594<br>(57.0%)<br>11) Infants HIV<br>positive at 9<br>months: 27/338<br>(8.0%) | 10) 1.18 (1.08-<br>1.29)<br><br>11) 0.92 (0.55-<br>1.53) | 11) AOR 0.89<br>(0.56,1.43) |
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303 Findings of the narrative synthesis are outlined below first as intervention types within  
304 intervention target categories (patient, provider, system) and then by PMTCT outcome.

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306 Synthesis of findings according to intervention type and target:

307 Patient Level Interventions:

308 Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of  
309 bias ranged from 3 to 6 of 6 criteria rated as high or unclear. Ezeanolue et al. (27) included 40  
310 clusters and 3,024 patients and evaluated a complex intervention that included monthly baby  
311 showers at participating churches where expectant mothers participated in educational games,  
312 received 'mama packs' containing supplies needed during delivery (sterile gloves, alcohol  
313 swabs, clean razor, etc.) and laboratory testing, and were given a contact point for follow-up.

314 Women in the intervention group were found to be significantly more likely to complete linkage  
315 to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI  
316 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks  
317 postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided

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3 318 pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at  
4  
5 319 home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss  
6  
7  
8 320 et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT  
9  
10 321 intervention compared to standard care. They found no statistically significant difference in  
11  
12 322 PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant  
13  
14 323 blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and  
15  
16 324 evaluated whether conditional cash transfers improved adherence, acceptance of and retention in  
17  
18 325 PMTCT services to 6 weeks postpartum. They found women in the intervention group were  
19  
20 326 significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have  
21  
22 327 attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95%  
23  
24 328 CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.  
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31 330 Patient/Provider Level Interventions:  
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33 331 One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention  
34  
35 332 directed at both patients and providers in which peer mentors were trained to provide in person  
36  
37 333 education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31).  
38  
39 334 They found patients in the intervention group were significantly less likely to adhere to ARTs  
40  
41 335 during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-  
42  
43 336 0.74]). No statistically significant effects were found on the remaining outcomes including: ART  
44  
45 337 use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART  
46  
47 338 post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were  
48  
49 339 unable to reach authors for additional information on long term outcomes.  
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3 341 Provider Level Interventions:  
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5 342 Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day  
6  
7 343 PMTCT knowledge and skills training course for nurses and midwives compared to standard  
8  
9 344 training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They  
10  
11 345 found a statistically significant increase in the proportion of women with ART detected in cord  
12  
13 346 blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).  
14  
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19 348 Provider/System Level Interventions:  
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21 349 Five studies reported interventions directed at both the provider and health system level  
22  
23 350 (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-  
24  
25 351 Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated  
26  
27 352 transmission of HIV test results to clinic staff via short message service (SMS), and ongoing  
28  
29 353 support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring  
30  
31 354 and addressing clinic underperformance). There was a trend towards an increase in the  
32  
33 355 proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.  
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40 357 Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess  
41  
42 358 the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing  
43  
44 359 (MIP+SMS) combined with integrated care against standard care (SOC). They found no  
45  
46 360 significant difference in maternal retention in care at 12 months in either intervention group  
47  
48 361 relative to controls using study definitions, or ministry of health definitions for retention. They  
49  
50 362 found no statistically significant difference in infant retention in care at 12 months in either  
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363 intervention group relative to controls using study definitions, or ministry of health definitions  
364 for retention .

365  
366 Oyeledun et al. (35) compared a continuous quality improvement intervention including  
367 coaching visits and collaborative meetings to standard ministry of health support in 32 clusters  
368 and 511 patients. They found no significant difference in retention in care at 6 months, in  
369 initiation of ART prophylaxis in infants within 72 hours of birth, or in proportion of women  
370 initiated on ARTs within 2 weeks of enrolment. They found significantly improved rates of  
371 infant HIV testing at 6-10 weeks (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-  
372 2.42]).

373  
374 Phiri et al. (36) conducted a 3-arm cluster RCT with 21 clusters and 1269 women evaluating  
375 facility-based peer support (FBPS) and community-based peer support (CBPS) from expert  
376 mothers against standard of care (SOC). They found non-significant improvement with FBPS  
377 and small statistically significant improvements with CBPS in uptake of ARTs (RR= 1.12 [95%  
378 CI 1.06-1.18]; ARD 0.09 [95% CI 0.01-0.18]), retention in care at 1 year (RR=1.01 [95% CI  
379 0.92-1.10]; ARD= 0.08 [95% CI 0.04-0.20]), and retention in care at 2 years (RR= 1.42 [95% CI  
380 1.22-1.65]; ARD=0.16 [95% CI 0.03-0.30]), relative to SOC. Retention in care at 2 years was  
381 significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-  
382 1.43]) using ministry of health definitions for retention in care. Infant HIV testing at 6 weeks was  
383 significantly higher in the CBPS only (RR=1.23 [95% CI 1.11-1.38]). There was no difference in  
384 infant HIV positive rates at 6 weeks in either intervention group.

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3 386 Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased  
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5 387 training of community health workers and increased home visits by community health workers  
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7 388 during and post delivery to provide PMTCT counselling and newborn care. They found a  
8  
9 389 significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention  
10  
11 390 group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in  
12  
13 391 mother to child HIV transmission at 12 weeks.  
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### 19 393 System Level Interventions:

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21 394 Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias  
22  
23 395 ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or  
24  
25 396 unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services  
26  
27 397 including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and  
28  
29 398 community involvement through male champions, compared to standard care across 12 clusters  
30  
31 399 and 369 patients. They found significant improvement in the proportion of eligible women  
32  
33 400 started on ART for PMTCT (RR= 2.47 [95% CI 2.07-2.95]; ARR 3.3 [95% CI 1.4-7.8]), and in  
34  
35 401 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI  
36  
37 402 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-  
38  
39 403 19.7]).  
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47 405 Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and  
48  
49 406 evaluated the impact of integration of HIV and maternal child health services during both  
50  
51 407 antenatal and postnatal periods. They found no improvement in the proportion of women  
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3 408 receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48  
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5 409 hours and the proportion of HIV positive infants.  
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10 411 Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual  
11  
12 412 care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a  
13  
14 413 statistically significant increase in the proportion of eligible women receiving ARTs during  
15  
16 414 pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).  
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21 416 Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during  
22  
23 417 pregnancy and post-delivery. They found statistically significant improvements in maternal  
24  
25 418 antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks  
26  
27 419 (RR= 1.08 [1.00-1.16]).  
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33 421 Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in  
34  
35 422 addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in  
36  
37 423 the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14];  
38  
39 424 AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the  
40  
41 425 intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no  
42  
43 426 significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal  
44  
45 427 NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.  
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51 429 Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters  
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53 430 in 3 countries, including 1876 patients. They found no significant improvement in the proportion  
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3 431 of pregnant women receiving ARTs (RR= 1.07 [95% CI 1.00- 1.14]) or infants tested for HIV by  
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5 432 6-8 weeks (RR= 1.23 [95% CI 1.09-1.40]).  
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8 433  
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10 434 Turan et al. (25) included 12 clusters and 1172 patients and examined the effects of integration  
11  
12 435 of HIV and antenatal care compared with standard non-integrated care. Self-reported maternal  
13  
14 436 ART use across the PMTCT spectrum, pre, during, and post delivery, was not significantly  
15  
16 437 different between groups, although it was significantly higher during pregnancy (RR=  
17  
18 438 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]). ART use was significantly lower among  
19  
20  
21 439 intervention sites during labor delivery RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI  
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23 440 0.04, 0.68] and post-delivery (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]). Infant  
24  
25 441 ART use after birth was significantly lower in intervention sites (RR= 0.41 [95% CI 0.32-0.54];  
26  
27 442 AOR= 0.18 [95% CI 0.09-0.35]), although infant HIV testing was increased at 6 weeks, and 9  
28  
29 443 months in intervention sites, the difference was not statistically significant. No difference was  
30  
31 444 found for infant HIV infection rates at 6 weeks, or 9 months.  
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37 446 Synthesis of findings according to PMTCT outcomes:  
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39 447 The vast majority of studies reported short-term PMTCT outcomes with ART use during  
40  
41 448 pregnancy (10/18) and labor and delivery (6/18), infant prophylaxis at birth (6/18), and infant  
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43 449 HIV testing at 6-10 weeks (5/18). Overall, findings are often mixed and effect sizes small, with  
44  
45 450 many of uncertain clinical significance.  
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51 452 Five studies found significant improvements in ART use during pregnancy ranging with RR  
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53 453 ranging from 1.12 to 2.48 (25, 26, 27, 36, 38). Effective interventions included: integration of  
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3 454 ANC and HIV services (RR= 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]) (25) and (RR=  
4  
5 455 2.28 [95% CI 1.86-2.80] AOR= 2.01 [95% CI 1.37-2.95]) (26); monthly baby showers at  
6  
7 456 participating churches providing education through games, ‘mama packs’ containing delivery  
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9 457 supplies, laboratory testing, and a contact point for follow-up (RR 1.56 [95% CI 0.93-2.62],  
10  
11 458 AOR=2.8 [95% CI 1.02-4.79]) (27); community based peer support from mentor mothers (RR=  
12  
13 459 1.12 [95% CI 1.06-1.18], ARR 0.09 [95% CI 0.01-0.18]) (36) ; and an integrated package of  
14  
15 460 PMTCT services including point-of-care CD4 testing, decentralized PMTCT care, integrated  
16  
17 461 mother/infant services, and community champions, (RR= 2.47 [95% CI 2.07-2.95], ARR 3.3  
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19 462 [95% CI 1.4-7.8]) (38). Four studies evaluating: staff training and support to ante-natal clinics,  
20  
21 463 and automated SMS transmission of HIV test results to clinic staff (33); a quality improvement  
22  
23 464 initiative (35); community health worker ante- and post-natal home visits (41); and facility level  
24  
25 465 systems analysis and improvement intervention (42), found no significant difference in ART use  
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27 466 during pregnancy. One study evaluating peer mentor led educational meetings, found ART  
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29 467 adherence during pregnancy lower in the intervention group (31).  
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31 468  
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38 469 Six studies reported ART use during labor and delivery, with 4/6 finding no significant effect  
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40 470 (29, 31, 39, 41)), 1 finding a significant but small improvement RR=1.17 (32) and 1 finding  
41  
42 471 significantly reduced ART use in the intervention group RR=1.614 (25). The one study that  
43  
44 472 found a small significant effect employed a 1-day PMTCT knowledge and skills training course  
45  
46 473 for nurses and midwives (RR= 1.17 [95% CI 1.08-1.26]) (32). Ineffective interventions included;  
47  
48 474 couples based PMTCT intervention (29), peer mentor led educational meetings (31), integration  
49  
50 475 of maternal child health and HIV services (39), and community health worker ante-natal and  
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52 476 post-partum home visits (41). In contrast to the findings for ART use during pregnancy, ART  
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3 477 use during labor and delivery was low significantly lower with integration of ANC and HIV care  
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5 478 (25) RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI 0.04, 0.68] (25).  
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10 480 Only 1 study evaluated ART use in the post-partum period and found significantly reduced ART  
11  
12 481 use during this period (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]) with integration of  
13  
14 482 ANC and HIV care (25). Two additional studies evaluated uptake across the cascade, with  
15  
16 483 conditional cash transfer found to significantly improve uptake of PMTCT recommendations  
17  
18 484 (RR= 1.26 [95% CI 1.08-1.48]) (30) and no difference found for integration of ANC and HIV  
19  
20 485 services (25).  
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26 487 Six studies evaluated infant HIV prophylaxis at birth. One of 6 studies reported a small  
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28 488 significant improvement in infant HIV prophylaxis at birth with community health worker home  
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30 489 visits (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) ( 41), 1/6 significantly  
31  
32 490 reduced infant prophylaxis at birth with integration of ANC and HIV care (RR= 0.41 [95% CI  
33  
34 491 0.32-0.54]; AOR= 0.18 [95% CI 0.09-0.35]) (25) and 4/6 studies finding no significant  
35  
36 492 difference with take home nevirapine dosing (28), peer mentor led educational meetings (31), a  
37  
38 493 quality improvement intervention (35), and integration of maternal child health and HIV services  
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40 494 during both the ante-natal and postpartum periods (39).  
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46  
47 496 Seven studies reported infant HIV testing at 6 weeks. Three of 7 found significantly improved  
48  
49 497 rates of infant testing by 6-10 weeks of age with RR ranging from 1.08 to 1.93 (35,37,40), 3/7  
50  
51 498 no difference (25, 41,42), and one study finding a mixed effect of peer support (36).  
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54 499 Improvements in infant HIV testing were found for a quality improvement intervention  
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3 500 (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-2.42]) (35), increased training of and  
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5 501 home visits from community health workers (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI  
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7 502 0.97-1.25]) (37), and SMS texts to patients both antenatally and post-delivery (RR= 1.08 [1.00-  
8  
9 503 1.16]) (40). One study found mixed effects of peer support on infant HIV testing, with  
10  
11 504 community based peer support found to significantly improve infant HIV testing at 6 weeks  
12  
13 505 (RR=1.23 [95% CI 1.11-1.38]) and no difference found for facility based peer support (36). No  
14  
15 506 difference was found for integration of ANC and HIV care (25), home visits from community  
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17 507 health workers (41) or a facility level analysis and quality improvement intervention (42).  
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19 508  
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22  
23 509 Outcome definitions for retention in care and infant HIV-positive rates were highly variable,  
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25 510 ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other  
26  
27 511 PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for  
28  
29 512 retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant  
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31 513 retention in care at 6 weeks, with 2 studies evaluating conditional cash transfers (30) and an  
32  
33 514 integrated package of PMTCT services including point-of-care CD4 testing, decentralized care,  
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35 515 integrated mother/infant services, and community champions (38), finding significantly  
36  
37 516 improved retention (RR= 1.11 [95% CI 1.00-1.23]) and at 6 weeks (RR= 9.44 [95% CI 5.60-  
38  
39 517 15.4]; ARR=9.1 [95% CI 5.2-15.9]) (38), and a third employing monthly baby showers finding  
40  
41 518 no difference (27).  
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49 520 Four studies examined infant HIV-positive rates at 6 weeks post-partum. Evaluated interventions  
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51 521 included; integration of ANC and HIV care (25), couples based HIV/PMTCT counselling (29),  
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53 522 conditional cash transfers (30), and peer support (36). All found no difference.  
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3 523  
45 524 **Discussion:**

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8 525 Eighteen studies were included in our review. Heterogeneity of interventions and outcome  
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10 526 reported limited both comparison across studies and intervention categories, as well as,  
11  
12 527 opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias,  
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14 528 primarily due to limitations inherent to health systems research and unclear reporting of key  
15  
16 529 methodological factors.  
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21 531 Based on our review findings, several interventions appear promising. In the single meta-  
22  
23 532 analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use  
24  
25 533 during pregnancy with integration of HIV and antenatal care compared to standard non-  
26  
27 534 integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies  
28  
29 535 found small positive effects of integration of HIV and antenatal care, alone or as part of a  
30  
31 536 complex intervention, on ART use during pregnancy. However, the effects of integration on  
32  
33 537 PMTCT outcomes during labor and delivery, and post-delivery were less clear, with no  
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35 538 difference found for some studies (39, 34) and for some outcomes (25), and one study finding  
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37 539 reduced ART use during labor and delivery, and post-delivery (25). Therefore, as integrated care  
38  
39 540 is increasingly common future work focusing on how integration of maternal child health and  
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41 541 HIV care may be optimized alone or in combination with other interventions to optimize  
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43 542 PMTCT outcomes beyond the antenatal period is needed.  
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51 544 Four studies evaluating different approaches to outreach services alone or in combination with  
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53 545 other interventions found small positive effects on linkage to care, ART use during pregnancy  
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3 546 and labor/delivery, and early infant HIV testing. Two studies found positive effects of role  
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5 547 expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy  
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7 548 and, when combined with outreach services, positive effects were seen on long term retention in  
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9 549 care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT  
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11 550 outcomes, each in a single study, included: educational meetings, conditional cash transfers,  
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13 551 continuous quality improvement, and use of information and communication technology.  
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18  
19 553 An important finding of the present review is the high degree of variability in outcome  
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21 554 definitions and relative lack of longer-term outcome data. While in some instances variability of  
22  
23 555 outcome definitions may be considered a strength where both self-report and biological markers  
24  
25 556 of ART use are included, variability in timing of outcomes limits comparison across studies and  
26  
27 557 opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the  
28  
29 558 findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is  
30  
31 559 clearly critical to reducing HIV transmission, longer term outcomes are equally important to  
32  
33 560 understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of  
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35 561 future work would be substantially improved through both standardization of timing of PMTCT  
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37 562 outcomes and through funding opportunities that would allow for evaluation of longer term  
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39 563 outcomes.  
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47 565 In keeping with other systematic reviews focused on interventions aimed at improving PMTCT  
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49 566 care and outcomes published to date (8,9,13,14,15), our review found the evidence base available  
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51 567 to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor  
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53 568 Car et al. (9), which included a single study and found -improved ART use in labor/delivery from  
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3 569 integration of care, our single meta-analysis including 2 studies found a positive effect of  
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5 570 integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only  
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8 571 2 of which met inclusion criteria for the present review, and they also found variable effects of  
9  
10 572 non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al.  
11  
12 573 (14) included 10 articles, with 2 overlapping studies included in our review, and focused on  
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14 574 postpartum retention of women in PMTCT and ART care. This latter review, which included  
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16 575 both high and LMICs and a broader range of study designs, focused on a limited portion of the  
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18 576 PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone  
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21 577 interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to  
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23 578 improve PMTCT service delivery and promote retention. Their review was conducted over a  
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26 579 similar timeframe to the present review, however, it differs from the present review in its  
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28 580 inclusion of high income country studies, inclusion of a range of study designs, and in its  
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31 581 approach to categorization of interventions. Thirty-four studies were included in their review, 11  
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33 582 of which were included in the present review. They found weak evidence for improvement of  
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35 583 early infant HIV diagnosis from mobile-phone based interventions and for male involvement in  
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38 584 reducing infant HIV transmission.

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42 586 Given the focus of the present review on providing evidence-based guidance to PMTCT program  
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44 587 planners and implementers based LMICs our review differs from the reviews noted above in  
45  
46 588 several ways. First, to optimize the quality of evidence we limited our review to randomized and  
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48 589 non-randomized controlled trials and interrupted times series studies. Second, to increase the  
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50 590 applicability of findings to LMIC implementers, we limited our review to studies conducted in  
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52 591 LMICs. Third, we included a broad range of intervention categories and included both maternal  
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3 592 and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to  
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5 593 provide information of direct relevance to implementation planning, we categorized and  
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8 594 analyzed interventions at both the level at which they are implemented (patient, provider,  
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10 595 system) and using the EPOC intervention classification scheme, which groups interventions  
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12 596 based on the intervention process/activities employed.  
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19 599 Limitations:

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21 600 While agreement on data extraction was not calculated, an initial calibration exercise was carried  
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23 601 out to ensure consistency in data extraction. Following this, comparison of completed data  
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25 602 extraction forms revealed few differences. Although no study was excluded for language, it is  
26  
27 603 possible that use of translation software may have resulted in exclusion of an eligible study due  
28  
29 604 to inaccurate translation. Additionally, while unlikely to have led to a significant difference in  
30  
31 605 results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO  
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33 606 as the later was not accessible to the second information technologist.  
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40 608 The multifaceted nature of the majority of interventions evaluated and variability in PMTCT  
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42 609 outcomes reported, limited our ability to combine studies statistically and to separate  
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44 610 effective/ineffective features of the interventions. In addition, efforts to contact authors for data  
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46 611 necessary for risk ratio calculations was ineffective in several cases. Due to the small number of  
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48 612 studies included in the meta-analysis publication bias could not be examined. Additionally,  
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50 613 although pre-specified in our protocol, interpretation of findings, most commonly infant HIV  
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52 614 infection rates, are limited by lack of power to assess secondary outcomes among included  
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3 615 studies. As 7 of the 18 studies limited participation to women 17-18 years of age or older, results  
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5 616 may be less generalizable to younger mothers. Finally, although the EPOC search filter is  
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7 617 designed to identify articles from all low- and middle-income countries, only articles from Sub-  
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9 618 Saharan Africa were included in the review. Results therefore may be less generalizable to  
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11 619 LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the  
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13 620 evidence to date and where funding should be targeted for future research based on knowledge  
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15 621 users needs.  
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22 623 *Future Directions:*

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24 624 Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were  
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26 625 generally small and often mixed across studies, and based on a small number of studies that were  
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28 626 largely at moderate to high risk of bias. Further research is needed both to improve quantity and  
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30 627 quality of data. First, replication of promising approaches is needed. Second, improved  
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32 628 publication reporting to ensure key methodological factors are addressed and to provide detail on  
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34 629 the likely impact of factors that cannot be modified through design. This transparency in  
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36 630 reporting will enhance interpretation and utility of findings in informing PMTCT policy and  
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38 631 program decision making. For example, while the nature of designs for evaluating PMTCT  
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40 632 interventions, often make blinding of participants impossible, description of the context and  
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42 633 likely impact would aid interpretation. Additionally, use of blinded outcome assessment or  
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44 634 objective outcomes such as laboratory confirmation of ART in blood samples will increase study  
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46 635 impact. Third, given the inherent difficulties in evaluating complex interventions, increased use  
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48 636 of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would  
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50 637 be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade and  
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638 longer term outcomes in particular where feasible, would allow for increased comparison across  
639 interventions.

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641 **Conclusions:**

642 The body of evidence synthesized in this review and in the literature to date on effectiveness of  
643 interventions to improve uptake and retention of mothers and infants in PMTCT care is limited  
644 by low quality evidence. A single meta-analysis of 2 studies employing integration of antenatal  
645 and HIV care suggested a potential for improvement of ART use during pregnancy based on  
646 weak evidence. Overall findings are mixed and effect sizes small and of uncertain clinical  
647 significance. In order to improve the utility of evidence to program planners future studies  
648 should strive to include key outcomes across the range of the PMTCT cascade where feasible,  
649 reduce risk of bias where possible and improve reporting of key methodological factors to allow  
650 for improved assessment of risk of bias and understanding of the likely impact of risk of bias  
651 where it cannot be addressed in design.

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653 **List of abbreviations:** ANC: Antenatal care; ART: Anti-Retroviral Therapy; AZT: Zidovudine,  
654 EPOC: Effective Practice and Organization of Care; HAART: Highly active antiretroviral  
655 therapy, HIV: Human Immunodeficiency Virus; LMIC: Low and Middle Income Country;  
656 MeSH: Medical Subject Headings; MOH: Ministry of Health; NVP: Nevirapine, PMTCT:  
657 Prevention of mother to child transmission of HIV; RCT: Randomized controlled trial; SMS:  
658 Short message service; SOC: Standard care; Versus: vs.

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660 **Declarations:**

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3 661 **Ethics approval and consent to participate:** Not applicable.  
4

5 662 **Consent for publications:** Not applicable.  
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7  
8 663 **Availability of data and material:** No additional data available.  
9

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11

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13

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15

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17

18 668 Diseases (P30 AI50410 and R01 AI131060-01).  
19

20 669 **Competing Interests:** The authors have declared that no competing interests exist. The authors  
21

22 670 alone are responsible for the writing and content of the paper.  
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28 672 **Authors' contributions:** LPR and MvL conceived the study. LPR and SS developed the search  
29

30 673 strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of  
31

32 674 article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence  
33

34 675 tables and manuscript. LPR conducted the meta-analysis with support from BP, MCH, NER, SP,  
35

36 676 ML, and FC provided content expertise and assisted with preparation of the protocol and  
37

38 677 manuscript. All authors provided critical revision of the manuscript and read and approved the  
39

40 678 final manuscript.  
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48

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12 801 and retention in prevention of mother-to-child HIV transmission care: A randomised controlled  
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40 813 improve access to antenatal CD4 testing and ART initiation in HIV-infected pregnant women: A  
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6 822 intervention on retention-in-care at 6 months postpartum in a PMTCT program in northern  
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8 823 Nigeria: Results of a cluster randomized controlled study. *J Acquir Immune Defic Syndr.*  
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19 828 child transmission program: A 3-arm cluster randomized controlled trial (PURE Malawi). *J*  
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21 829 *Acquir Immune Defic Syndr.* 2017;75:S140-8.  
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31 833 mother-to-child transmission of HIV in a South African township. *Trop Med Int Health.*  
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42 838 in rural north-central Nigeria: A cluster-randomised controlled trial. *Lancet HIV.* 2016;3:e202-  
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3 841 39- Geelhoed D, Lafort Y, Chissale É, et al. Integrated maternal and child health services in  
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5 842 Mozambique: Structural health system limitations overshadow its effect on follow-up of HIV-  
6  
7 843 exposed infants. *BMC Health Serv Res.* 2013;13:207.  
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12 845 40- Odeny TA, Bukusi EA, Cohen CR, et al. Texting improves testing: A randomized trial of  
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14 846 two-way SMS to increase postpartum prevention of mother-to-child transmission retention and  
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16 847 infant HIV testing. *AIDS.* 2014;28:2307-2312.  
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21 849 41- Rotheram-Borus MJ, Tomlinson M, Le Roux IM, et al. A cluster randomised controlled  
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23 850 effectiveness trial evaluating perinatal home visiting among South African mothers/infants. *PLoS*  
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34 855 Mozambique: A cluster randomized trial. *J Acquir Immune Defic Syndr.* 2016;72:e68-76.  
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40 857 **Captions for appended Tables and Figures:**

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42 858

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44 859 Table 1: Characteristics of Included Studies

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46 860 Table 2: Results of Included Studies

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48 861 Figure 1: PRISMA diagram of search results and screening

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50 862 Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to  
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52 863 usual (non-integrated care) effect on ART use during pregnancy  
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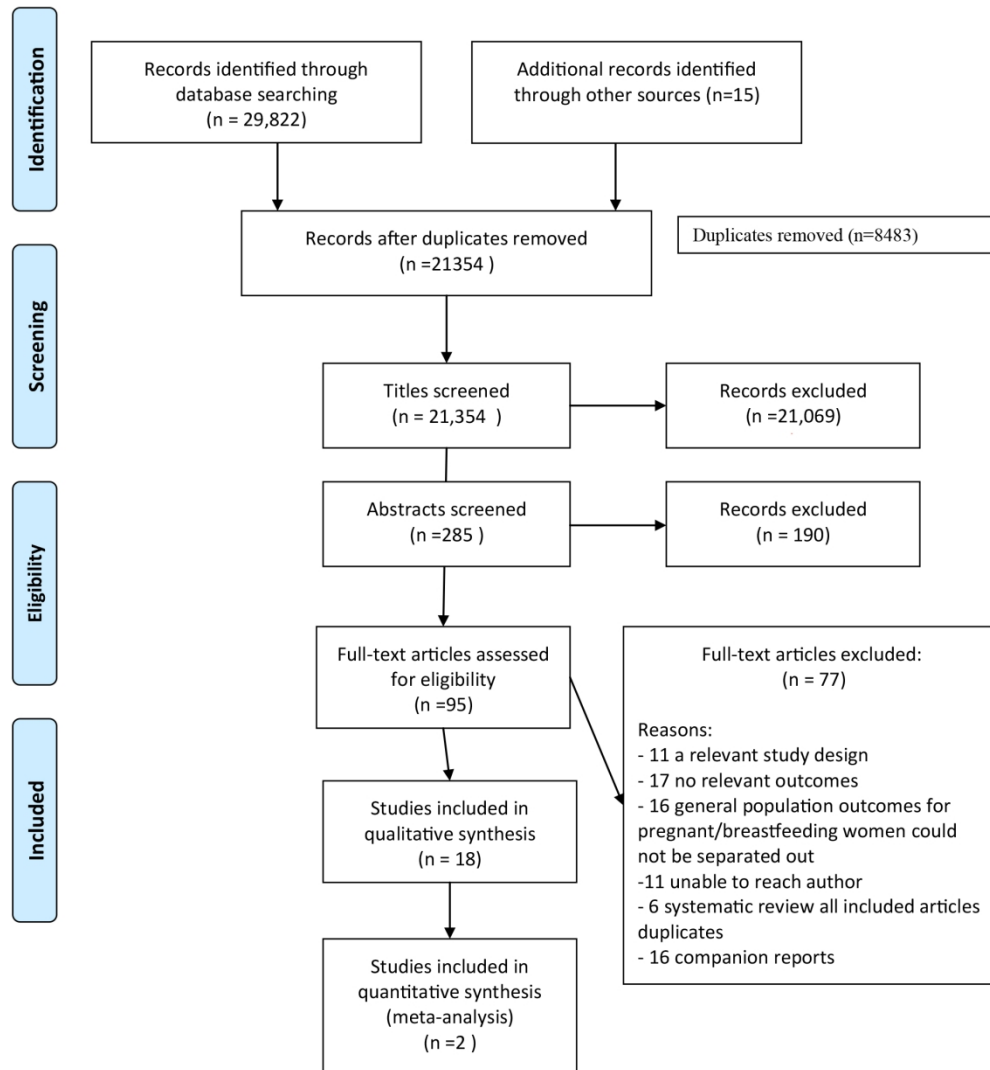


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

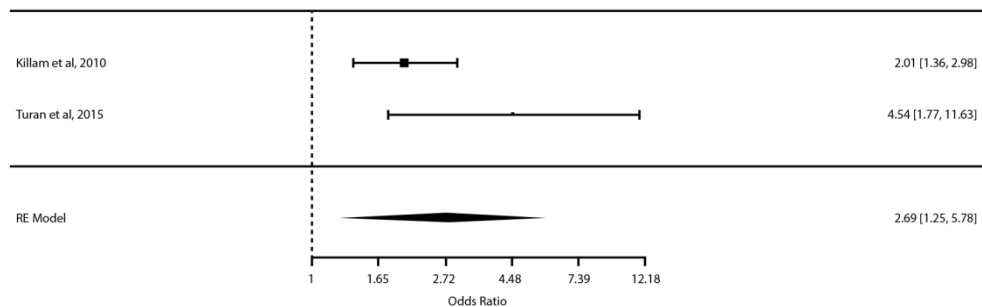
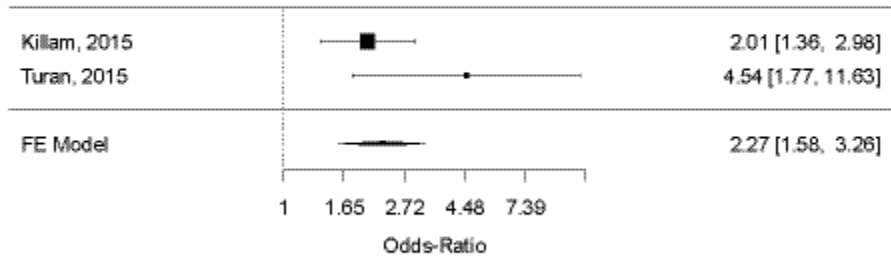


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

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8 Pregnant / Breastfeeding Women

- 9 1 Pregnant Women/ (5226)  
10 2 exp Breast Feeding/ (26666)  
11 3 Milk, Human/ (15697)  
12 4 Infectious Disease Transmission, Vertical/ (12256)  
13 5 fetus/ (68631)  
14 6 exp pregnancy/ (723003)  
15 7 peripartum period/ (427)  
16 8 exp Postpartum Period/ (49233)  
17 9 exp pregnancy complications/ (345863)  
18 10 exp Maternal Health Services/ (35913)  
19 11 pregnan\*.mp,kw,kf. (778553)  
20 12 gestat\*.tw,kw,kf. (144054)  
21 13 breastfeed\*.mp,kw,kf. (13469)  
22 14 (breast adj2 feed\*).mp,kw,kf. (30938)  
23 15 (breast adj2 milk).mp,kw,kf. (8972)  
24 16 breastmilk.tw,kw,kf. (683)  
25 17 human milk.tw,kw,kf. (7840)  
26 18 lactat\*.mp,kw,kf. (165010)  
27 19 (milk adj2 eject\*).tw,kw,kf. (704)  
28 20 (milk adj2 let\*-down).tw,kw,kf. (68)  
29 21 ((expectant or expecting) adj2 wom#n).mp,kw,kf. (182)  
30 22 parturit\*.tw,kw,kf. (11506)  
31 23 birth\*.mp,kw,kf. (259925)  
32 24 childbirth\*.mp,kw,kf. (14074)  
33 25 child-birth\*.mp,kw,kf. (491)  
34 26 deliver\*.mp,kw,kf. (474171)  
35 27 puerper\*.mp,kw,kf. (21074)  
36 28 breastfed.tw,kw,kf. (3524)  
37 29 mtct.tw,kw,kf. (559)  
38 30 pmtct.tw,kw,kf. (725)  
39 31 (vertical adj2 transmission\*).tw,kw,kf. (4511)  
40 32 f?etus\*.mp,kw,kf. (137278)  
41 33 f?etal.mp,kw,kf. (302029)  
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3 34 (breast adj2 fed\*).tw,kw,kf. (5276)  
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5 35 in-utero.tw,kw,kf. (20490)  
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7 36 (intrauterine or intra-uterine).tw,kw,kf. (42420)  
8  
9 37 (trans-placent\* or transplacent\*).tw,kw,kf. (5212)  
10  
11 38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)  
12  
13 39 (parent\* adj2 (child\* or infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (28605)  
14  
15 40 mother\*.tw,kw,kf. (147803)  
16  
17 41 (nursing adj2 (infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (1319)  
18  
19 42 (prenatal\* or pre-natal\*).tw,kw,kf. (70920)  
20  
21 43 (perinatal\* or peri-natal\*).tw,kw,kf. (51747)  
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23 44 (post-natal\* or postnatal\*).tw,kw,kf. (85370)  
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25 45 (antenatal\* or antenatal\*).tw,kw,kf. (23135)  
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27 46 (antepartum\* or ante-partum\*).tw,kw,kf. (4566)  
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29 47 (postpartum\* or post-partum\*).tw,kw,kf. (40829)  
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31 48 maternal\*.tw,kw,kf. (172644)  
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33 49 or/1-48 (1763167)

#### HIV/AIDS

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- 50 exp HIV Infections/ (233689)
  - 51 exp HIV/ (83825)
  - 52 HIV Long-Term Survivors/ (607)
  - 53 AIDS Serodiagnosis/ (6107)
  - 54 hiv.mp,kw,kf. (263320)
  - 55 Human T-Cell Leukemia Virus.mp,kw,kf. (2850)
  - 56 htlv-iii.mp,kw,kf. (1652)
  - 57 (acquired adj2 immun\* adj2 (syndrome\* or virus\*)).mp,kw,kf. (86030)
  - 58 (human\* adj2 immun\* adj2 deficien\* adj2 virus\*).mp,kw,kf. (491)
  - 59 (human\* adj2 immun\* adj2 virus\*).mp,kw,kf. (76929)
  - 60 (syndrome\* adj2 lymphadenopath\*).tw,kw,kf. (335)
  - 61 slim disease.tw,kw,kf. (25)
  - 62 lymphadenopathy-associated virus\*.mp,kw,kf. (295)
  - 63 lav-htlv-iii.mp,kw,kf. (211)
  - 64 sbl-6669.mp,kw,kf. (16)
  - 65 lav-2.mp,kw,kf. (25)
  - 66 (acquired adj2 immun\* adj2 deficien\* adj2 syndrome\*).tw,kw,kf. (5057)
  - 67 (aids adj10 (disease\* or syndrome\*)).mp,kw,kf. (27876)

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3 68 (aids adj1 related).tw,kw,kf. (6614)

4 69 htlv\*.tw,kw,kf. (11427)

5 70 hiv###.mp,kw,kf. (1760)

6 71 or/50-70 (325026)

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10 Patient uptake / dropouts / participation

11 72 Patient Dropouts/ (6786)

12 73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)

13 74 exp Consumer Participation/ (32566)

14 75 dropout\*.tw,kw,kf. (6483)

15 76 (uptake or up-take).tw,kw,kf. (248330)

16 77 (drop\* adj1 out\$1).tw,kw,kf. (8228)

17 78 (refusal\* or refuse\$1 or refusing).tw,kw,kf. (23366)

18 79 (patient\* adj2 (elope or elope\$1 or eloping)).tw,kw,kf. (4)

19 80 (non complian\* or noncomplian\*).tw,kw,kf. (9990)

20 81 complian\*.tw,kw,kf. (84306)

21 82 (uncooperat\* or unco-operat\* or un-co-operat\*).tw,kw,kf. (1028)

22 83 (cooperat\* or co-operat\*).tw,kw,kf. (102475)

23 84 (non-accept\* or nonaccept\*).tw,kw,kf. (592)

24 85 accept\*.tw,kw,kf. (279089)

25 86 (nonparticipat\* or non-participat\*).tw,kw,kf. (1298)

26 87 participat\*.tw,kw,kf. (322007)

27 88 (nonadher\* or non-adher\*).tw,kw,kf. (10638)

28 89 adher\*.tw,kw,kf. (114637)

29 90 (retain\* or retention\*).tw,kw,kf. (244370)

30 91 (non-attend\* or nonattend\*).tw,kw,kf. (1453)

31 92 attend\*.tw,kw,kf. (110407)

32 93 (comply\* or complies or complian\*).tw,kw,kf. (91550)

33 94 (non-comply\* or noncomply\* or non-complian\* or noncomplian\*).tw,kw,kf. (10004)

34 95 reluctan\*.tw,kw,kf. (8504)

35 96 ((healthcare or care or advice or medical or information) adj3 seek\$3).tw,kw,kf. (15252)

36 97 (disengag\* or dis-engag\*).tw,kw,kf. (2812)

37 98 engag\*.tw,kw,kf. (82419)

38 99 avoid\*.tw,kw,kf. (237366)

39 100 ut.fs. (144195)

40 101 ignor\*.tw,kw,kf. (27215)

41 102 reject\*.tw,kw,kf. (82472)

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3 103 (non-embrac\* or nonembrac\*).tw,kw,kf. (0)  
4 104 (un-embrac\* or unembrac\*).tw,kw,kf. (1)  
5 105 (embrace\* or embracing).tw,kw,kf. (7691)  
6 106 (un-accept\* or unaccept\*).tw,kw,kf. (14546)  
7 107 (unadher\* or un-adher\*).tw,kw,kf. (14)  
8 108 no-show\*.tw,kw,kf. (484)  
9 109 (follow\* adj1 up).tw,kw,kf. (638770)  
10 110 incent\*.tw,kw,kf. (17823)  
11 111 enabl\*.tw,kw,kf. (214935)  
12 112 disincent\*.tw,kw,kf. (859)  
13 113 utiliz\*.tw,kw,kf. (319558)  
14 114 (inclin\* or disinclin\*).tw,kw,kf. (12034)  
15 115 or/72-114 (2984236)  
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24 Study type / characteristics  
25 116 randomized controlled trial.pt. (387105)  
26 117 exp Randomized controlled trial/ (387132)  
27 118 exp Randomized Controlled Trials as Topic/ (97414)  
28 119 clinical trial.pt. (490674)  
29 120 Double-Blind Method/ (128228)  
30 121 Placebos/ (32662)  
31 122 clinical trials as topic/ (171490)  
32 123 evaluation research/ (119973)  
33 124 program evaluation/ (47548)  
34 125 Feasibility Studies/ (45412)  
35 126 Pilot Projects/ (85700)  
36 127 Evaluation Studies as Topic/ (119973)  
37 128 Cost-Benefit Analysis/ (61646)  
38 129 (random\* or non-random\* or unrandom\* or nonrandom\*).mp,kw,kf. (874470)  
39 130 placebo\*.mp,kw,kf. (168179)  
40 131 rct\*1.tw,kw,kf. (17367)  
41 132 ((singl\* or doubl\* or trebl\* or tripl\*) adj1 (mask\* or blind\* or dumm\*)).mp,kw,kf. (176744)  
42 133 evaluat\*.mp,kw,kf. (2416275)  
43 134 effectiv\*.mp,kw,kf. (1149619)  
44 135 sustainab\*.mp,kw,kf. (23041)  
45 136 feasib\*.mp,kw,kf. (177882)  
46 137 appropriateness.mp,kw,kf. (12458)  
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3 138 efficac\*.mp,kw,kf. (507876)  
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6 140 (pilot adj2 (project\* or study or studies)).mp,kw,kf. (103303)  
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8 141 cost-effectiv\*.mp,kw,kf. (73309)  
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10 142 (cost\*1 adj2 benefit\*1).mp,kw,kf. (69472)  
11 143 (interrupt\* adj2 time).mp,kw,kf. (1224)  
12 144 or/116-143 (4705604)  
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14 Lower middle income countries

- 15 145 Developing Countries/ (63034)  
16 146 (Imic or Imics or lami countr\*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)  
17 147 ((developing or less\* developed or under developed or underdeveloped or middle income  
18 or low\* income or underserved or under served or deprived or poor\*) adj (countr\* or nation? or  
19 population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)  
20 148 (Afghan\* or Albania\* or Algeria\* or Angola\* or Antigua\* or Barbud\* or Argentin\* or  
21 Armenia\* or Aruba\* or Azerbaijan\* or Bahrain\* or Bangladesh\* or Barbad\* or Benin\* or Byelarus\*  
22 or Byelorus\* or Belarus\* or Belorus\* or Beliz\* or Bhutan\* or Bolivia\* or Bosnia\* or Herzegovin\* or  
23 Hercegovin\* or Botswan\* or Brasil\* or Brazil\* or Bulgaria\* or Burkina Faso\* or Burkina Fasso\* or  
24 Upper Volta\* or Burundi\* or Urundi\* or Cambodia\* or Khmer Republic or Kampuchea\* or  
25 Cameroon\* or Cameron\* or Cape Verde\* or Central African Republic or Chad\* or Chile\* or China  
26 or chinese or Colombia\* or Comoros\* or Comoro Islands or Comores or Mayott\* or Congo\* or  
27 Zair\* or Costa Rica\* or Cote d'Ivoire or Ivory Coast or Croatia\* or Cuba\* or Cyprus or cyprian or  
28 Czechoslovakia\* or Czech Republic or Slovakia\* or Slovak Republic or Djibouti\* or French  
29 Somaliland or Dominica\* or East Timor or East Timur or Timor Leste or Ecuador\* or Egypt\* or  
30 United Arab Republic or El Salvador\* or Eritrea\* or Estonia\* or Ethiopia\* or Fiji\* or Gabon\* or  
31 Gambia\* or Gaza\* or Georgia Republic or Georgian Republic or georgian or Ghana\* or Gold  
32 Coast or Greece or greek or Grenada\* or Guatemala\* or Guinea\* or Guam\* or Guiana\* or  
33 Guyana\* or Haiti\* or Hondura\* or Hungar\* or India\* or Maldiv\* or Indonesia\* or Iran\* or Iraq\* or  
34 Isle of Man or Jamaica\* or Jordan\* or Kazakh\* or Kenya\* or Kiribati\* or Korea\* or Kosovo\* or  
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40 Namibia\* or Nepal\* or Netherlands Antill\* or New Caledonia\* or Nicaragua\* or Niger\* or Northern  
41 Mariana Island\* or Oman\* or Muscat\* or Pakistan\* or Palau\* or Palestin\* or Panama\* or Paragua\*  
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3 Roumania\* or Russia\* or Rwanda\* or Ruanda\* or Saint Kitts\* or St Kitts or Nevis\* or Saint Lucia\*  
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5 Tome\* or Saudi Arabia\* or saudi or Senegal\* or Serbia\* or Montenegr\* or Seychelles or Sierra  
6 Leone or Slovenia\* or Sri Lanka\* or Ceylon\* or Solomon Islands or Somalia\* or South Africa\* or  
7 Sudan\* or Surinam\* or Swaziland or swazi or Syria\* or Tajik\* or Tadjik\* or Tadhik\* or Tanzania\*  
8 or Thailand or thai or Togo or Togolese Republic or Tonga\* or Trinidad\* or Tobag\* or Tunisia\* or  
9 Turkey or turkish or Turkmenistan\* or Turkmen\* or Uganda\* or Ukrain\* or Urugua\* or USSR or  
10 Soviet Union or Union of Soviet Socialist Republics or Uzbek\* or Vanuat\* or New Hebrides or  
11 Venezuela\* or Vietnam\* or Viet Nam\* or West Bank or Yemen\* or Yugoslavia\* or Zambia\* or  
12 Zimbabw\* or Rhodesia\* or cabo verd\*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)  
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18 149 or/145-148 (4677916)  
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21 Full topic

22 150 49 and 71 and 115 and 144 and 149 (3309)

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24 151 exp animals/ not (exp animals/ and exp humans/) (4003250)  
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26 Full topic minus animal-only studies

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### Risk of Bias within included studies

| Study                 | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting |
|-----------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|-----------------------------|
| Aliyu; 2016           | Low                        | Unclear                | High                                   | High                           | Low                     | Low                         |
| Dryden-Peterson; 2015 | Unclear                    | Low                    | High                                   | High                           | High                    | Low                         |
| Ezeanolue; 2015       | Low                        | Low                    | High                                   | Unclear                        | High                    | Low                         |
| Geelhoed; 2013        | Unclear                    | Unclear                | Unclear                                | Unclear                        | High                    | High                        |
| Kieffer; 2011         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Killam; 2010          | Unclear                    | High                   | High                                   | Unclear                        | High                    | Unclear                     |
| Mwapasa; 2017         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Low                         |
| Odeny; 2014           | Low                        | Low                    | High                                   | Unclear                        | Low                     | Unclear                     |
| Oyeledun; 2017        | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Phiri; 2017           | Unclear                    | High                   | High                                   | Low                            | Low                     | Low                         |
| Reynolds; 2010        | Unclear                    | Unclear                | High                                   | High                           | High                    | Unclear                     |
| Richter; 2014         | Unclear                    | High                   | High                                   | High                           | High                    | Low                         |
| Rotheram-Borus; 2014  | Unclear                    | Unclear                | High                                   | High                           | Unclear                 | Low                         |
| Rustagi; 2016         | Low                        | Unclear                | Unclear                                | Unclear                        | Unclear                 | Low                         |
| Tomlinson; 2014       | Low                        | Unclear                | High                                   | Low                            | Low                     | Low                         |
| Turan; 2015           | Low                        | High                   | High                                   | High                           | High                    | Low                         |
| Weiss; 2014           | Unclear                    | Unclear                | Unclear                                | Unclear                        | Unclear                 | High                        |
| Yotebieng; 2016       | Low                        | Unclear                | High                                   | High                           | High                    | High                        |



# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page # |
|------------------------------------|----|---|--------------------|
| <b>TITLE</b>                       |    |   |                    |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | 1                  |
| <b>ABSTRACT</b>                    |    |   |                    |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4                |
| <b>INTRODUCTION</b>                |    |   |                    |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | 5-6                |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 6                  |
| <b>METHODS</b>                     |    |   |                    |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | 7                  |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 7                  |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 8                  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | 8                  |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 8-9                |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 8-9                |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | 9                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 10                 |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | 10                 |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.   | 10                 |





# PRISMA 2009 Checklist

Page 1 of 2

| Section/topic                 | #  | Checklist item   | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | 10                 |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | N/A                |
| <b>RESULTS</b>                |    |  |                    |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Figure 1           |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | 11-12<br>Table 1   |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 12-13<br>Table 2   |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 14-20<br>Table 3   |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 13<br>Figure 2     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 10                 |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | N/A                |
| <b>DISCUSSION</b>             |    |  |                    |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | 20-23              |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 4, 23              |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 24                 |
| <b>FUNDING</b>                |    |  |                    |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | 25                 |



# PRISMA 2009 Checklist

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For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

# BMJ Open

## 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-024907.R3   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 11-May-2019  |
| Complete List of Authors:       | Puchalski Ritchie, LM; University of Toronto, Department of Medicine, Division of Emergency Medicine; Li Ka Shing Knowledge Institute, St. Michael's Hospital, Knowledge Translation Program<br>van Lettow, Monique; Dignitas International; University of Toronto Dalla Lana School of Public Health<br>Pham, Ba; Li Ka Shing Knowledge Institute, St. Michael's Hospital<br>Straus, Sharon; St. Michael's Hospital, Li Ka Shing Knowledge Institute; University of Toronto, Department of Medicine<br>Hosseinipour, Mina C.; University of North Carolina, Division of Infectious Disease; University of North Carolina Project<br>Rosenberg, Nora; University of North Carolina; University of North Carolina Project<br>Phiri, Sam; University of North Carolina, Department of Health Behavior, School of Public Health; Lighthouse Trust<br>Landes, Megan; University Health Network, Department of Emergency Medicine; University of Toronto, Department of Family and Community Medicine<br>Cataldo, Fabian; Dignitas International; University of Toronto, Dalla Lana School of Public Health |
| <b>Primary Subject Heading</b>: | HIV/AIDS   |
| Secondary Subject Heading:      | HIV/AIDS   |
| Keywords:                       | HIV, prevention of mother to child transmission, interventions, uptake, retention  |
|                                 |  |

SCHOLARONE™  
Manuscripts

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3 1 **What interventions are effective in improving uptake and retention of HIV-positive**  
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5 2 **pregnant and breastfeeding women and their infants in prevention of mother to child**  
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7 3 **transmission care programs in low- and middle- income countries? A systematic review**  
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10 4 **and meta-analysis**  
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15 6 Lisa M. Puchalski Ritchie<sup>1,2,3</sup>, Monique van Lettow<sup>4,5</sup>, Ba Pham<sup>2</sup>, Sharon E. Straus<sup>1,2</sup>, Mina C.  
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17 7 Hosseinipour<sup>6,7</sup>, Nora E. Rosenberg<sup>6,7,8</sup>, Sam Phiri <sup>6,9,10,11</sup>, Megan Landes<sup>3,4,12</sup>, Fabian Cataldo<sup>4,5</sup>;  
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19 8 For the PURE consortium  
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## Abstract

### Objective:

This review was conducted to identify interventions effective in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services in LMICs in order to inform program planning.

### Methods:

We conducted a systematic review of studies comparing usual care to any intervention to improve uptake and retention of HIV-positive pregnant or breastfeeding women and their children from birth to 2 years of age in PMTCT services in LMICs. Twenty-two electronic databases were searched from inception to January 15, 2018, for randomized, quazi-randomized, and non-randomized controlled trials, and interrupted time series studies; reference lists of included articles were searched for relevant articles. Risk of bias was assessed using the Cochrane Effective Practice and Organisation of Care Group criteria. Random effects meta-analysis was conducted for studies reporting similar interventions and outcomes.

**Results:** We identified 29,837 articles of which 18 studies were included in our review. Because of heterogeneity in interventions and outcome measures, only 1 meta-analysis of 2 studies and 1 outcome was conducted; we found a statistically significant increase in ART use during pregnancy for integration of HIV and antenatal care relative to standard non-integrated care (pooled AOR=2.69; 95% CI 1.25-5.78, P=0.0113). The remaining studies assessing other individual, provider, or health system interventions were synthesized narratively with small effects seen across intervention categories for both maternal and infant PMTCT outcomes based predominately on evidence with moderate to high risk of bias.

### Conclusions:

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3 69 The evidence on effectiveness of interventions to improve uptake and retention of mothers and  
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5 70 infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal  
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7 71 care may improve ART use during pregnancy. Future studies to replicate promising approaches  
8  
9 72 are needed. Improved reporting of key methodological criteria will facilitate interpretation of  
10  
11 73 findings and improve the utility of evidence to PMTCT program planners.  
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14  
15 74 **Systematic review registration:** PROSPERO-CRD42015020829  
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17 75 **Key Words:** HIV, prevention of mother to child transmission, interventions, retention, uptake  
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26 79 **Strengths and Limitations of this review:**  
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- 28 80 • A comprehensive search was conducted, including grey literature sources and hand  
29  
30 81 searching.  
31  
32 82 • A broad range of intervention categories, as well as, both maternal and infant outcomes  
33  
34 83 from across the spectrum of the PMTCT cascade were included.  
35  
36 84 • Our search was limited to studies conducted in low- and middle-income countries in  
37  
38 85 order to increase utility of findings to LMIC PMTCT programmers  
39  
40 86 • The multifaceted nature of the interventions and variability in outcomes reported, limited  
41  
42 87 our ability to combine studies statistically.  
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44 88 • Due to the small number of studies included in the meta-analysis publication bias could  
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46 89 not be examined.  
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54 91 **Introduction:**  
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3 92 In 2015, 150,000 new HIV infections and 110,000 HIV-related deaths occurred globally among  
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5 93 children <15 years of age, with mother to child transmission the leading cause of new HIV  
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7 94 infections among children (1,2). Despite effectiveness of prevention of mother to child  
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9  
10 95 transmission (PMTCT) of HIV regimens (3,4), uptake of and retention in PMTCT care remains  
11  
12 96 below target in many low and middle-income countries (LMICs) (4,5,6). While progress has  
13  
14 97 been made in understanding barriers to uptake and retention of women and their infants in  
15  
16 98 PMTCT services (7), evidence to provide guidance to LMIC implementers and policy makers  
17  
18 99 seeking to optimize PMTCT services remains limited.  
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21  
22 100  
23  
24 101 Eight systematic reviews have been conducted on strategies to optimize PMTCT. Two of these  
25  
26 102 reviews evaluated the effectiveness of interventions, specifically, male involvement (8) and  
27  
28 103 integration of services (9), to improve coverage of PMTCT services. These reviews were limited  
29  
30 104 by the lack of studies to provide recommendations. A third review (10) examined the effects of  
31  
32 105 integration of antenatal care with postnatal and other health services for a broad range of  
33  
34 106 maternal health outcomes in LMICs; although some PMTCT studies and outcomes were  
35  
36 107 included, this was not the focus of the review. A fourth systematic review evaluated  
37  
38 108 interventions for improving initiation of antiretroviral therapy (ART) therapy in pregnant women  
39  
40 109 (11) and found the evidence quality insufficient to support recommendations. A fifth systematic  
41  
42 110 review (12) assessed the impact of China's PMTCT cascade in improving uptake and outcomes  
43  
44 111 at various steps along the cascade; specific interventions implemented to operationalize the  
45  
46 112 cascade were not reported. Three systematic reviews have been published since the initiation of  
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48 113 the present review. One review evaluated non-pharmacological interventions to improve quality  
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50 114 of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of  
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3 115 included studies reported PMTCT outcomes, this was not a primary focus of the review. A  
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5 116 second review focused on postpartum retention of women in PMTCT and ART care (14). This  
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7 117 review focused on a limited portion of the PMTCT cascade. A third review (15) focused on  
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9 118 interventions to improve PMTCT service delivery and promote retention. This review included a  
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11 119 range of study designs and studies conducted in both high and low-middle income countries and  
12  
13 120 as such, is of less value as a guide to decision making for PMTCT policy and programming in  
14  
15 121 LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by:  
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17 122 lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade  
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19 123 and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high  
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21 124 income country studies where the context of PMTCT care is often substantially different than in  
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23 125 LMICs.  
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31 127 This review was developed in collaboration with knowledge users from the Malawi Ministry of  
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33 128 Health's HIV treatment and care technical working group. The objective of this current review  
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35 129 was to identify what interventions at the patient, provider, or health system level are effective  
36  
37 130 compared to no intervention or usual care in improving uptake and retention of HIV-positive  
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39 131 mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health  
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41 132 services in LMICs, this review is targeted to provide guidance for PMTCT policy and  
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43 133 programming in LMICs, and therefore included a broad range of intervention categories, as well  
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45 134 as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.  
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54 137 **Methods:**  
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3 138 *Protocol:* A protocol was developed for this review based on the Cochrane Handbook for  
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5 139 systematic reviews (16) and the Cochrane Effective Practice and Organisation of Care Group  
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7 140 (EPOC) (17) and registered with PROSPERO (CRD42015020829, available at:  
8  
9 141 [http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42015020829#](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020829#).  
10  
11 142 VXHCNUZBn5I). The complete protocol was previously published and the methods are  
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13 143 presented briefly here (18). Our findings are reported using the PRISMA statement for reporting  
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15 144 systematic reviews (19).  
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21 146 *Patient and Public Involvement:*

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24 147 No patients were involved in this study.  
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28 149 *Eligibility Criteria:*

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30 150 We included studies reporting the effectiveness of interventions in improving uptake and/or  
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32 151 retention of HIV-positive pregnant or breast feeding women and their children from birth to 2  
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34 152 years of age or termination of breast feeding in PMTCT services. We included randomized,  
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36 153 quasi-randomized and non-randomized controlled trials, and interrupted time series studies that  
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38 154 compared usual care or no intervention to any type of intervention at the patient, provider, or  
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40 155 health system level. Although included in error in the Prospero registration for our review,  
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42 156 controlled before and after studies were not included in the protocol manuscript or search.  
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44 157 Studies were included if conducted in LMICs as defined by the EPOC filter (20) and updated  
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46 158 using the most recent World Bank World Country and Lending group classification (21). Studies  
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48 159 that included both high and low/middle- income countries were eligible for inclusion if LMICs  
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3 160 results could be abstracted. No restriction was placed based on language of publication,  
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5 161 publication status, study time frame, or duration of follow-up.  
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10 163 *Information Sources and Literature Search:*  
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12 164 A search strategy was developed in consultation with an experienced information specialist  
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14 165 (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review  
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16 166 of Electronic Search Strategies checklist (22). The following databases were searched from  
17  
18 167 inception to July 31, 2015 and subsequently updated using the same search strategy for the  
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20 168 period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV,  
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22 169 pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and  
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24 170 retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global  
25  
26 171 Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science,  
27  
28 172 Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE,  
29  
30 173 ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library,  
31  
32 174 WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov.  
33  
34 175 Several databases planned for inclusion in our search were no longer available or not accessible  
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36 176 by our group at the time of the search and were therefore not included: AIDS Education Global  
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38 177 Information System, British Library Catalogue, and the New York Academy of Grey Literature.  
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40 178 In addition, we searched reference lists of included articles, and contacted several experts in the  
41  
42 179 field to inquire about eligible unpublished or in progress studies. See supplementary file for  
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44 180 complete MEDLINE search strategy.  
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54 182 *Study Selection and Data Collection Process:*  
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3 183 A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a  
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5 184 sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement.  
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7 185 Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then  
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9 186 abstracts were screened, and second, the full-text articles were screened. Translation software  
10  
11 187 was utilized to screen articles at the titles and abstracts level, with no non-English articles  
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13 188 remaining at the full article review phase. A data abstraction form was created using the EPOC  
14  
15 189 data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in  
16  
17 190 screening and data extraction. A calibration exercise was conducted with completed data  
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19 191 extraction forms compared and discussed for each of the first 3 articles to ensure consistency;  
20  
21 192 data extraction was then completed for the remaining articles independently and in duplicate by 2  
22  
23 193 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each  
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25 194 study included: population, intervention, comparator, context, outcomes, study design, time  
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27 195 frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes  
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29 196 were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment,  
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31 197 percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis,  
32  
33 198 and percentage of women and infants retained in PMTCT care/completing the ART regimen as  
34  
35 199 defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of  
36  
37 200 infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants  
38  
39 201 completing post-exposure HIV testing 6 weeks following termination of breast feeding for all  
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41 202 infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV;  
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43 203 adverse events; major or minor congenital malformations; small for gestational age; pre-mature  
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45 204 delivery; still birth; and infant death within first 2 years of life (18).  
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3 206 When necessary to clarify published data or to obtain unpublished data, we contacted primary  
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5 207 authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions,  
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8 208 and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to  
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10 209 calculate risk ratios were not available in the publication. Three responded and provided the  
11  
12 210 requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional  
13  
14 211 data as they were submitting the manuscript for publication.  
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19 213 Methodological Quality/Risk of Bias Appraisal:

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21 214 Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the  
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23 215 Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies  
24  
25 216 included in the meta-analysis, risk of publication bias could not be examined using funnel plots.  
26  
27 217 Selective reporting bias was assessed through review of trial registrations where available and  
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29 218 categorized as unclear if not registered.  
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35 220 Data Synthesis:

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37 221 Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy  
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39 222 for health system interventions and discrepancies resolved through discussion (23). Clinical  
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41 223 heterogeneity was determined based on patient, intervention, and outcome characteristics.  
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43 224 Descriptive synthesis of study results were conducted for all studies, and are reported narratively  
44  
45 225 and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate  
46  
47 226 intervention effects using the Metafor Package in the statistical software R (24). Statistical  
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49 227 heterogeneity was examined using the  $I^2$  statistic, with  $I^2 \geq 75\%$  indicating significant  
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51 228 heterogeneity (16).  
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**Results:**Literature Search:

A total of 29,837 articles were identified through the database and hand search. After duplicates were removed 21,354 titles and abstracts were screened and 95 articles reviewed in full. Thirty-four articles representing 18 studies with 16 companion reports met eligibility criteria (Figure 1, flow diagram).

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Study Characteristics:

Study characteristics are outlined in Table .

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Table 1: Characteristics of Included Studies

| Author (s); Year | Intervention Level/Type | Study Design                              | Country ; Geographic Location in Country          | Study Population  | Intervention   | Comparison | Intervention Classification EPOC            | Number of Participants     | Participant Characteristics   | Outcomes   |
|------------------|-------------------------|---|---|---|--|------------|---|----------------------------|---|--|
| Ezeanolue; 2015  | Patient                 | Mixed Methods Including Small Cluster RCT | Nigeria (Enugu state)                             | Self-identified pregnant women $\geq 18$ years who attended any church site | Monthly baby showers offered health education and onsite laboratory testing including HIV testing, and Mama Packs for essential items during pregnancy | Usual care | • Outreach services                         | 40 churches, 3002 patients | • % HIV positive: 2% overall<br>• Maternal age (mean): I = 29.3, C = 29.7 | 1) ART during pregnancy<br>2) Retention in care at 6-8 week postpartum |
| Reynolds; 2010   | Patient                 | Cluster RCT                               | Kenya (Coast, Rift Valley, and Western provinces) | HIV-positive pregnant women $\geq 18$ and at least 32 weeks gestation       | PMTCT providers trained to prepare and counsel women on how to   | Usual care | • Self-management<br>• Educational outreach | 10 Clusters: 160 patients  | • Maternal age (mean): I = 27.4, C = 28.4                                 | Infant ART prophylaxis at birth  |

|                 |                  |             |  |  |  |  |                                     |                            |  |  |
|-----------------|------------------|-------------|--|--|--|--|-------------------------------------|----------------------------|--|--|
|                 |                  |             |  |  | store and administer take-home nevirapine infant dose  |  |                                     |                            |  |  |
| Weiss; 2014     | Patient          | RCT         | South Africa (Gert Sibande and Nkangala districts) | HIV-positive pregnant women, 24 to 30 weeks gestation, and ≥18 years of age, recruited and asked to invite their male partner to enroll as a couple. | 4 successive weekly sessions employed a cognitive-behavioral approach and addressed HIV, safer sex, sexual negotiation, and PMTCT issues. Sessions were closed, structured, of gender-concordant groups, led by trained gender-matched facilitators, and conducted in ANCs.                          | Time-matched health education sessions | • Group (couple) vs individual care | 12 Clusters<br>478 couples | • % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive<br>• Maternal age (mean): I = 28.3; C = 28.1 | 1) ART detected in mother blood samples at birth<br>2) ART detected in infants blood at birth<br>3) Infant HIV-positive rate at 6 weeks            |
| Yotebieng; 2016 | Patient          | RCT         | Democratic Republic of Congo (Kinshasa)            | Newly diagnosed HIV-positive women, <=32 weeks gestation, registering for ANC  | Participants received small escalating cash payments, starting at US \$5 and increasing by \$1 each visit. If attended scheduled clinic appointments and completed recommended actions. Incentive reset to its original value if mother failed to complete any actions required at a specific visit. | Usual care                             | • Conditional cash transfer         | 433 women                  | • Maternal age (median): I= 29.5, C = 29.0   | 1) Retention in care at 6 weeks postpartum<br>2) Uptake of PMTCT services through to 6 weeks postpartum<br>3) Infant HIV-positive rates at 6 weeks |
| Richter, 2014   | Patient/Provider | Cluster RCT | South Africa                                       | HIV-positive women,  | 8-session intervention   | Usual care                             | • Role expansion                    | 8 Clusters                 | • Maternal age   | 1) ART from  |

|                         |                 |                        |                     |   |  |            |   |                             |  |   |
|-------------------------|-----------------|------------------------|---------------------|---|--|------------|---|-----------------------------|--|---|
|                         |                 |                        | (KwaZulu-Natal)     | ≥18 years of age and <34 weeks pregnant   | conducted by peer mentors (4 antenatal, 4 postnatal) to support HIV-positive women through pregnancy and early motherhood. HIV-positive women recruited, trained and certified as peer mentors prior to implementation; in-person supervision was provided weekly. |            | or task shifting<br>• Educational meetings                                      | 1200 patients               | (mean): (I = 26.5; C = 26.5)   | the 28th week of pregnancy (AZT or HAART)<br>2) ART during labor (AZT or HAART)<br>3) NVP or HAART during labor<br>4) Infant NVP at birth<br>5) AZT dispensed for infant and medication as prescribed |
| Kieffer; 2011           | Provider        | Cluster RCT            | Swaziland           | All pregnant women presenting for delivery at participating maternity facilities        | 1-day training course provided to nurse-midwives to increase knowledge and skills in provision of PMTCT and to enhance confidence and counseling skills.   | Usual care | • Educational meetings  | 6 Clusters<br>2444 Patients | % HIV positive at enrollment: 33% overall  | NVP in cord blood   |
| Dryden - Petersen; 2015 | Provider/System | Step wedge Cluster RCT | Botswana (Gaborone) | ART-naïve, HIV-positive women registering at antenatal clinic before 26 weeks gestation | 2-hour clinical staff education sessions on protocols for CD4 testing; open-source platform permitting automated SMS to monitor/deliver CD4 results between central labs and clinics; longitudinal support for tracing   | Usual care | • The use of information and communication technology<br>• Educational meetings | 19 Clusters<br>336 women    | % HIV positive: I = 189 (47.6%) and C = 177 (44.6%)<br>• Maternal age (median): (I = 28; C = 29) | ART initiation by 30 wks gestation  |



|                |                 |                    |  |   |   |   |  |   |   |  |
|----------------|-----------------|--------------------|--|---|---|---|--|---|---|--|
|                |                 |                    |  |   | women eligible for ART initiation   |   |  |   |   |  |
| Mwapa sa; 2017 | Provider/System | 3 Arm, Cluster RCT | Malawi (Salima and Mangochi districts)     | HIV-positive pregnant women initiated on Option B+ regimen  | MIP-integration of HIV/ANC, routine tracing<br><br>MIP + SMS, integrated HIV/ANC care, SMS sent to community health worker to trace if appointment missed | Usual care: non-integrated care, routine tracing as for MIP | <ul style="list-style-type: none"> <li>Integration</li> <li>The use of information and communication technology</li> </ul> | 30 Clusters<br>1350 women   | <ul style="list-style-type: none"> <li>Maternal age (median): MIP = 29.5; MIP+SMS = 29.2; SOC = 29.4</li> </ul> | 1) Maternal retention in care at 12 months postpartum trial data<br>2) Infant retention in care at 12 months postpartum trial data<br>3) Maternal retention in care at 12 months using MOH definition<br>4) Infant retention in care at 12 months using MOH definition |
| Oyeledun; 2017 | Provider/System | Cluster RCT        | Northern Nigeria (Benue and Kaduna states) | HIV-positive, women, gestational age <= 34 weeks, who were ART naive and agreed to start lifelong ART | QI teams established, visits by coaches and collaborative meetings  | Routine MOH support   | <ul style="list-style-type: none"> <li>Continuous quality improvement</li> </ul>   | 32 Clusters: (6 later excluded)<br>532 women (21 withdrew leaving 511 in total) | <ul style="list-style-type: none"> <li>Maternal age (median): I = 27 ; C = 27</li> </ul>                        | 1) ART initiated within 2 week of enrolment<br>2) Retention in care at 6 months<br>3) Infants starting prophylaxis within 72 hours<br>4) infant HIV testing  |

|             |                 |                    |  |   |   |   |  |                           |   |   |
|-------------|-----------------|--------------------|--|---|---|---|--|---------------------------|---|---|
|             |                 |                    |  |   |   |   |  |                           |   | at 6-10 weeks   |
| Phiri; 2017 | Provider/System | 3 Arm, Cluster RCT | Malawi (SE, SW and Central West Zones) | Pregnant and breastfeeding HIV-positive women and their infants. Up to 3 male sex partners could be enrolled per patient. | FBPS - women received SOC and met with "mentor mothers", HIV-positive women who had recently completed PMTCT and were on ART. Mentor mothers provided 1-on-1 support at each clinic visit, led weekly clinic-based support groups, and contacted women within 1 week of a missed appointment.<br><br>CBPS- women received SOC and met with "expert mothers", HIV-positive women who recently completed PMTCT and were on ART. Expert mothers conducted routine home visits to provide HIV education and clinic visit reminders, and led monthly community-based support group meetings. | SOC = standard of care facilities provided routine HIV care according to Malawi MOH guidelines. According to national guidelines, women who fail to attend the clinic within 60 days of a missed appointment are supposed to be traced. However, this rarely occurs in the routine program. | • Role expansion or task shifting outreach services<br>• The use of information and communication technology | 21 Clusters<br>1269 women | • Maternal age (median across all 3 arms): 27 | 1) ART uptake<br>2) Retained in care at 1 year:<br>3) Retained in care at 2 years trial data<br>4) Retained in care at 2 years MOH definition<br>5) Infant HIV tested at 6 weeks<br>6) Infant HIV-positive at 6 weeks |

|                  |                 |             |   |   |   |  |  |                             |  |  |
|------------------|-----------------|-------------|---|---|---|--|--|-----------------------------|--|--|
|                  |                 |             |   |   | Expert mothers were responsible for contacting women in the community within 1 week of a missed clinic visit.   |  |  |                             |  |  |
| Tomlins on; 2014 | Provider/System | Cluster RCT | South Africa (Umlazi)                     | Pregnant women aged $\geq 17$ and their newborns residing in the clusters during the recruitment period   | CHWs were trained to carry out structured home visits using motivational interviewing for breastfeeding counseling. Women were scheduled to receive 7 home-based visits during pregnancy and post-delivery. Low birth weight neonates received 2 extra visits within the first week | In control clusters, CHWs provided information and support on accessing social welfare grants and conducted three home-based visits: during pregnancy and post-delivery.               | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Outreach services</li> </ul>                     | 30 Clusters<br>3957 women   | Maternal age (median): I = 23; C = 23  | 1) Infant HIV testing by 6 weeks<br>2) Infant HIV-positive at 12 weeks   |
| Aliyu; 2016      | System          | Cluster RCT | Rural north-central Nigeria (Niger State) | HIV-positive women and their infants, presenting for ANC or delivery who met 1 of following criteria: unknown HIV status at presentation; history of ART prophylaxis or treatment, but not receiving ARTs at presentation; or known | Integrated package of PMTCT services that included point-of-care CD4 cell count or percentage testing, transition of decentralized PMTCT tasks to trained midwives, integrated mother and infant care services, active influential family member (male                              | Standard of care included health information, opt-out HIV testing, infant feeding counseling, referral for CD4 cell counts and treatment, ART prophylaxis, and early infant diagnosis. | <ul style="list-style-type: none"> <li>• Role expansion /task shifting</li> <li>• Integration</li> <li>• Packages of care</li> </ul> | 12 Clusters<br>369 patients | <ul style="list-style-type: none"> <li>• Maternal age (median): I = 26 ; C = 28</li> </ul> | 1) Maternal ART initiation<br>2) Maternal-infant retention in care at 6 week postpartum<br>3) Maternal-infant retention in care at 12 weeks postpartum |

|                |        |                        |                            |   |  |            |   |                              |  |  |
|----------------|--------|------------------------|----------------------------|---|--|------------|---|------------------------------|--|--|
|                |        |                        |                            | HIV status but had never received treatment   | partner) participation, and community involvement (male community peer champions providing outreach, education, and linkage of male partners to key referral services) |            |   |                              |  |  |
| Geelhoed; 2013 | System | Cluster RCT            | Mozambique (Tete province) | Public primary health facilities providing maternal child health and PMTCT services Mothers and their children up to 5 years of age.              | Reorganized services to deliver integrated consultations and services for mothers and their children up to 5 years of age.   | Usual care | <ul style="list-style-type: none"> <li>Integration</li> <li>Educational meetings</li> </ul>           | 6 Clusters                   | Not available  | 1) ART in labor:<br>2) Infants receiving prophylaxis within 48 hours<br>3) Infant HIV-positive |
| Killam; 2010   | System | Step wedge Cluster RCT | Zambia (Lusaka)            | ART eligible pregnant women presenting at participating clinics   | Integration of ART care into ANC. Women already receiving ART at the general ART clinic encouraged to continue receiving their services in the general ART clinic      | Usual care | <ul style="list-style-type: none"> <li>Integration</li> </ul>   | 8 Clusters<br>31536 patients | <ul style="list-style-type: none"> <li>% HIV positive: I = 21.8%; C = 22.2%</li> <li>Maternal age (mean): I = 27.5; C = 27.3</li> </ul>  | ART initiation during pregnancy  |
| Odeny; 2014    | System | RCT                    | Kenya (Nyanza region)      | HIV-positive women attending antenatal or HIV care; $\geq 18$ years of age; between 28 weeks gestation and delivery; enrolled in PMTCT; access to | Custom-built, automated software to send and receive text messages. Sent 14 text messages, up to 8 sent during pregnancy, and weekly for first 6 weeks                 | Usual care | <ul style="list-style-type: none"> <li>The use of information and communication technology</li> </ul> | 388 Patients                 | <ul style="list-style-type: none"> <li>% HIV positive: 29.3% (388/1324)</li> <li>Maternal age (mean): (I = 30.8% 18-24, 56.9% 25-34, 12.3% 35+; C = 33.7% 18-24, 57.5% 25-34, 8.8% 35+)</li> </ul> | 1) Maternal postpartum clinic attendance to 8 weeks<br>2) Infant HIV testing by 8 weeks        |



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|--|--|--|--|--|---|---|--|--|--|---|
|  |  |  |  |  | and continuing until a definitive pediatric HIV diagnosis was obtained or the child reached 18 months of age. | to a separate HIV clinic at the same facility |  |  |  | birth 5) ART use through out all 3 PMTCT periods 6) Infant HIV testing by 3 months 7) Infant HIV testing at 9 months 8) Infants HIV tested by 6 weeks 9) Infants HIV-positive at 6 weeks 10) Infants HIV tested by end of study (up to 12 months ) 11) Infants HIV-positive at 9 months |
|--|--|--|--|--|---|---|--|--|--|---|

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243 The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge

244 design, and 2 RCTs. The number of clusters ranged from 6 to 40, and participants across all

245 study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan

246 Africa between 2005 and 2016. Half of included studies reported multifaceted interventions

247 including 2 or more EPOC category components [9/18] and as a result several were categorized

248 at more than 1 intervention level: patient [4], provider [1], system [7], patient/provider [1], or

249 provider/system [5]. Interventions directed all or in part to the health system level were most

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2  
3 250 common [12/18]. Integration [5/18], role expansion or task shifting [5/18], outreach services  
4  
5 251 [4/18], and use of information and communication technology [4/18] were the most common  
6  
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8 252 EPOC intervention categories employed alone or as part of a complex intervention.  
9

10 253  
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12 254 Reporting of population characteristics varied widely across studies as did outcome definitions.  
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14 255 Seven studies limited participation to pregnant women 17-18 years of age or older; median ages  
15  
16 256 across the studies ranged from 23 to 29.7 years. Marital status was reported in 14 studies, and  
17  
18 257 varied widely from 9% to 99% of women who were married or had a live-in partner. Maternal  
19  
20 258 education level was reported in 12 studies; 5 studies reported the majority of women having no  
21  
22 259 or primary education, 5 studies reported the majority of women having received secondary  
23  
24 260 education, and, 2 reported mean/median years of education [10.3 years, 10 years [range 8-  
25  
26 261 12years]]. Maternal employment [6/18] and parity [2/18] status were reported in a minority of  
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29 262 studies (Table 1). No pre-specified adverse events were reported in the identified studies.  
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35 264 Reported outcomes varied substantially across studies, with few studies within intervention  
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37 265 categories reporting comparable outcomes. For example, 5 studies reported interventions  
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39 266 employing integration alone [2] or in combination with other interventions [3], with only 1  
40  
41 267 PMTCT outcome in common among the 2 studies employing integration alone. The most  
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43 268 commonly reported outcomes were maternal ART use during pregnancy and labor and delivery,  
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45 269 infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.  
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49 270  
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51 271 As a result of the multifaceted nature of the majority of interventions employed, and variability  
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53 272 in PMTCT outcomes reported, the ability to combine results statistically was limited.  
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274 Methodological Quality:

275 Risk of bias was assessed using the Cochrane EPOC risk of bias criteria (17). Five of the 18  
276 studies were appraised as low risk of bias on 3 or more (4 with 3, 1 with 4) of the 6 main criteria.  
277 The most common issues encountered were unclear reporting of randomization (8/18) and  
278 allocation concealment (11/18), and unclear reporting or high risk of bias due to lack of blinding  
279 of participants/personnel (18/18) and blinding of outcome assessment (16/18) (The complete risk  
280 of bias table is included as an additional file).

281

282 Meta-analysis of Effect of Integration of care on ART use during pregnancy:

283 We expected variation in the implementation of integrated care of ART therapy into ANC in the  
284 two studies, conducted in clinics in Zambia and Kenya. We also expected some variation in  
285 standard care in the two settings, particularly with respect to eligibility and timing of ART  
286 initiation across the two studies both of which experienced policy changes during the course of  
287 the study. We therefore used a random-effects meta-analysis to derive the combined effect  
288 estimate of integrated care based on theoretical grounds although the  $I^2$  was not significant.  
289 Two studies assessing integration of HIV and antenatal care relative to usual non-integrated care  
290 were combined in a meta-analysis of 1,887 patients (25,26); there was increased use of ARTs  
291 during pregnancy with integration of HIV and antenatal care compared to standard non-  
292 integrated care, non-integrated care, (AOR=2.69; 95% CI=1.25, 5.78; P=0.0113,  $I^2=59.26\%$ )  
293 (Figure 2) (see supplementary file for fixed effects meta-analysis diagram) .

294

295 Descriptive Synthesis:



296 Details of included studies (country, intervention, population characteristics, outcomes, etc.) are  
 297 outlined in Table 1. Outcomes according to level(s) of intervention and according to PMTCT  
 298 outcome are outlined in Tables 2 and 3 respectively.

299

300 Table 2: Results of Included Studies by Level of Intervention

| Author: Year    | Intervention Level | Intervention Classification EPOC                 | Intervention   | Control                                 | Outcomes Intervention Group  | Outcomes Control Group  | Risk Ratio (95%CI)   | Adjusted Statistic where provided                          |
|-----------------|--------------------|--|--|---|--|---|--|--|
| Ezeanolue; 2015 | Patient            | • Outreach services                              | Monthly baby showers   | Usual care                              | 1) ART during pregnancy: 24/41 (65%)<br>2) Retention in care at 6-8 week postpartum: 33/41(81%)  | 1) ART during pregnancy: 12/32 (50%)<br>2) Retention in care at 6-8 week postpartum: 28/32(88%)   | 1) 1.56 (0.93 - 2.62)<br>2) 0.92 (0.75- 1.12)                        | 1) AOR 2.8 (1.02-4.79)<br>2) AOR 0.39 (0.04-3.99)          |
| Reynolds; 2010  | Patient            | • Self-management<br>• Educational outreach      | Take home infant nevirapine dose   | Usual care                              | Infant ART prophylaxis at birth: 80/85 (94%)   | Infant ART prophylaxis at birth: 66/75 (88%)  | 1.07 (0.97- 1.18)  | --   |
| Weiss; 2014     | Patient            | • Group (couple) vs. individual care             | Couples HIV risk reduction and PMTCT education sessions                    | Time matched general education sessions | 1) ART detected in mother blood samples at birth: 9/12 (75%)<br>2) ART detected in infants blood at birth: 12/13 (92%)<br>3) Infant HIV positive at 6 weeks:1/30 (3.3%)                    | 1) ART detected in mother blood samples at birth: 16/12 (50%)<br>2) ART detected in infants blood at birth: 9/12 (75%)<br>3) Infant HIV positive: 3/39 (7.7%)                               | 1) 1.50 (0.78- 2.88)<br>2) 1.23 (0.86- 1.77)<br>3) 0.43 (0.05- 3.96) | --   |
| Yotebieng; 2016 | Patient            | • Conditional cash transfer                      | Cash payments for clinic attendance and acceptance of recommended services | Usual Care                              | 1) Retention in care at 6 weeks postpartum: 174/216 (80.6%)<br>2) Uptake of PMTCT services through to 6 wks postpartum:146/216 (67.6%)<br>3) HIV positive infants at 6 weeks: 5/169 (3.0%) | 1) Retention in care at 6 weeks postpartum: 157/217 (72.4%)<br>2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%)<br>3) HIV positive infants at 6 weeks: 6/156 (3.9%) | 1) 1.11(1.00- 1.23)<br>2) 1.26(1.08- 1.48)<br>3) 0.77(0.24- 2.47)    | 1) ARD 1.13 (1.02-1.26)<br>2) ARD 1.31 (1.12-1.54)<br>3) – |
| Richter, 2014   | Patient/Provider   | • Role expansion or task shifting<br>• Education | Peer Mentor led educational meetings                                       | Usual Care                              | 1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%)<br>2) ART during labor (AZT or HAART):  | 1) ART from the 28th week of pregnancy (AZT or HAART): 455/466 (95.5%)<br>2) ART during labor (AZT or   | 1) 0.92 (0.89- 0.96)   | 1) AOR 0.44 (0.26,0.74)<br>2) AOR 1.16(0.44, 3.02)         |

|                        |                 |   |   |   |  |   |   |  |
|------------------------|-----------------|---|---|---|--|---|---|--|
|                        |                 | al meetings   |   |   | 282/377 (74.8%);<br>3) NVP or HAART during labor: 361/377 (95.8%)<br>4) Infant NVP at birth: 364/377 (96.6%)<br>5) AZT dispensed for infant and medicated as prescribed: 348/377 (92.3%)   | HAART):<br>334/466 (71.7%)<br>3) NVP or HAART during labor: 456/466 (97.9%)<br>4) Infant NVP at birth: 451/466 (96.8%)<br>5) AZT dispensed for infant and medicated as prescribed: 374/466 (80%)  | 2) 1.04 (0.96-1.13)<br>3) 0.98 (0.95-1.00)<br>4) 1.00 (0.97-1.02)<br>5) 1.15 (1.09-1.21)  | 3) AOR 0.53 (0.20, 1.41)<br>4) AOR 1.00 (0.36, 2.79)<br>5) AOR 2.98 (0.78,11.30)   |
| Kieffer ;2011          | Provider        | • Educational meetings  | 1 day PMTCT training for nurses and midwives  | No additional training                        | NVP in cord blood: 373/465(80%)  | NVP in cord blood: 325/472 (69%)  | 1.17 (1.08, 1.26)   | ---  |
| Dryden-Peters on; 2015 | Provider/System | • The use of information and communication technology<br>• Educational meetings | Staff training in point of care CD4 testing and automated SMS results reporting to staff, support for patient tracing           | Usual care                                    | ART initiated by 30 wks gestation: 56/154 (36.4%)  | ART initiated by 30 wks gestation: 37/153 (24.2%)   | 1.50 (1.06-2.13)  | AOR 1.06 (0.53,2.13)   |
| Mwapa; 2017            | Provider/System | • Integration<br>• The use of information and communication technology          | MIP= integration of antenatal and HIV care, routine patient tracing<br>MIP+SMS, integrated care and use of SMS enhanced tracing | Usual non-integrated care and patient tracing | 1) Maternal retention in care at 12 months postpartum trial data:<br>MIP 89/461(19.3%)<br>MIP+SMS 115/493(23.3%)<br>2) Infant retention in care at 12 months postpartum trial data:<br>MIP 32/386 (8.3%)<br>MIP+SMS 82/399 (20.1%)<br>3) Maternal retention in care at 12 months using MOH definition:<br>MIP 334/461 (72.4%)<br>MIP+SMS 332/493 (67%)<br>4) Infant retention in care at 12 months using MOH definition:<br>MIP 291/386 (75.4%)<br>MIP+SMS 323/399 (80.9%) | 1) Maternal retention in care at 12 months postpartum trial data:<br>SOC 90/396 (22.7%)<br>2) Infant retention in care at 12 months postpartum trial data:<br>SOC 32/300 (10.7 %)<br>3) Maternal retention in care at 12 months using MOH definition:<br>SOC 274/396 (69.1%)<br>4) Infant retention in care at 12 months using MOH definition:<br>SOC 234/300 (78.0%) | 1) MIP vs SOC 0.85 (0.65-1.10), MIP+SMS vs SOC 1.03 (0.81-1.31)<br>2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82)<br>3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06)<br>4) MIP vs SOC 0.97 (0.89-1.05), MIP+SMS vs SOC 1.04(0.96-1.12) | 1) MIP vs SOC ARR 0.85 (0.56-1.30), MIP+SMS vs SOC ARR 1.08 (0.87-1.35)<br>2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31)<br>3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05)<br>4) MIP vs SOC ARR 0.98 (0.89-1.09), MIP+SMS vs SOC ARR 1.01 (0.96-1.07) |

|                 |                 |  |  |  |  |  |   |   |
|-----------------|-----------------|--|--|--|--|--|---|---|
| Oyedun; 2017    | Provider/System | <ul style="list-style-type: none"> <li>Continuous quality improvement</li> </ul>   | <ul style="list-style-type: none"> <li>QI teams established, coaching, and collaborative meetings</li> </ul>   | Routine MOH support  | <p>1) ART initiated within 2 week of enrolment: 233/247 (94.3%)</p> <p>2) Retention in care at 6 months. 102/247 (41.3%)</p> <p>3) Infants starting prophylaxis within 72 hours : 138/209 (66%)</p> <p>4) Infant HIV testing at 6-10 weeks 102/209 (48.8%)</p>   | <p>1) ART initiated within 2 week of enrolment: 233/247 (94.3%)</p> <p>2) Retention in care at 6 months. 102/247 (41.3%)</p> <p>3) Infants starting prophylaxis within 72 hours : 138/209 (66%)</p> <p>4) Infant HIV testing at 6-10 weeks: 49/194 (25.3%)</p>   | <p>1) 1.05 (1.01-1.08)</p> <p>2) 1.07 (0.88-1.31)</p> <p>3) 0.88 (0.78-1.00)</p> <p>4) 1.93 (1.46-2.55)</p>   | <p>1) --</p> <p>2) ARR 1.08(0.78, 1.49)</p> <p>3) ARR 0.95 (0.84, 1.07)</p> <p>4) ARR 1.76(1.27, 2.42)</p>  |
| Phiri; 2017     | Provider/System | <ul style="list-style-type: none"> <li>Role expansion or task shifting outreach services</li> <li>The use of information and communication technology</li> </ul> | <ul style="list-style-type: none"> <li>FBPS – facility based peer support from mentor mothers</li> <li>CBPS- community based peer support from mentor mothers</li> </ul> | SOC- standard of care  | <p>1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%)</p> <p>2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%)</p> <p>3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394 (54%)</p> <p>4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%)</p> <p>5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%)</p> <p>6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%)</p> | <p>1) ART uptake: SOC- 361/447(81%)</p> <p>2) Retained in care at 1 year: SOC- 261/361 (74%)</p> <p>3) Retained in care at 2 years (trial data): SOC- 169/447 (38%)</p> <p>4) Retained in care at 2 years (MOH definition): SOC- 255/447(57%)</p> <p>5) Infant HIV test at 6 weeks: SOC- 169/273(62%)</p> <p>6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)</p> | <p>1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06-1.18)</p> <p>2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10)</p> <p>3) SOC vs FBPS 1.38(1.19-1.60), SOC vs CBPS 1.42 (1.22-1.65)</p> <p>4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43)</p> <p>5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38)</p> <p>6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09)</p> | <p>1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18)</p> <p>2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20)</p> <p>3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30)</p> <p>4) --</p> <p>5) --</p> <p>6) ---</p> |
| Tomlinson; 2014 | Provider/System | <ul style="list-style-type: none"> <li>Role expansion or task shifting</li> <li>Outreach services</li> </ul>   | <ul style="list-style-type: none"> <li>10 structured home visits from community health workers addressing PMTCT and newborn care</li> </ul>                              | <ul style="list-style-type: none"> <li>3 home visits from community health workers providing support in accessing social welfare grants</li> </ul> | <p>1) Infant HIV testing by 6 weeks: 420/571(73.6%)</p> <p>2) Infant HIV positive at 12 weeks: 28/568 (4.9%)</p>   | <p>1) Infant HIV testing by 6 weeks: 465/698(66.6%)</p> <p>2) Infant HIV positive at 12 weeks: 32/697 (4.6%)</p>   | <p>1) 1.10 (1.03-1.19)</p> <p>2) 1.07 (0.65-1.76)</p>   | <p>1) ARR 1.10 (0.97, 1.25)</p> <p>2) ARR 1.07 (0.69,1.66)</p>  |

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| 1  |                         |        |  |  |                           |   |  |   |   |
| 2  |                         |        |  |  |                           |   |  |   |   |
| 3  |                         |        |  |  |                           |   |  |   |   |
| 4  |                         |        |  |  |                           |   |  |   |   |
| 5  |                         |        |  |  |                           |   |  |   |   |
| 6  |                         |        |  |  |                           |   |  |   |   |
| 7  |                         |        |  |  |                           |   |  |   |   |
| 8  |                         |        |  |  |                           |   |  |   |   |
| 9  |                         |        |  |  |                           |   |  |   |   |
| 10 |                         |        |  |  |                           |   |  |   |   |
| 11 |                         |        |  |  |                           |   |  |   |   |
| 12 |                         |        |  |  |                           |   |  |   |   |
| 13 |                         |        |  |  |                           |   |  |   |   |
| 14 |                         |        |  |  |                           |   |  |   |   |
| 15 | Aliyu;<br>2016          | System | <ul style="list-style-type: none"> <li>• Role expansion /task shifting</li> <li>• Integration</li> <li>• Packages of care</li> </ul> | Integrated package of PMTCT services, family/male partner participation, community champions | Usual Care                | <p>1) Maternal ART initiation for PMTCT:166/172 (97%)</p> <p>2) Maternal-infant retention in care at 6 weeks postpartum: 125/150 pairs (83%)</p> <p>3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)</p>   | <p>1) Maternal ART initiation for PMTCT: 77/197 (39%),</p> <p>2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%)</p> <p>3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%)</p>  | <p>1) 2.47 (2.07-2.95)</p> <p>2) 9.44 (5.60-15.40)</p> <p>3) 11.40 (6.40-20.34)</p>   | <p>1) ARR 3.3 (1.4-7.8)</p> <p>2) ARR 9.1 (5.2-15.9)</p> <p>3) ARR 10.3(5.4-19.7)</p>   |
| 16 |                         |        |  |  |                           |   |  |   |   |
| 17 |                         |        |  |  |                           |   |  |   |   |
| 18 |                         |        |  |  |                           |   |  |   |   |
| 19 |                         |        |  |  |                           |   |  |   |   |
| 20 |                         |        |  |  |                           |   |  |   |   |
| 21 |                         |        |  |  |                           |   |  |   |   |
| 22 |                         |        |  |  |                           |   |  |   |   |
| 23 |                         |        |  |  |                           |   |  |   |   |
| 24 |                         |        |  |  |                           |   |  |   |   |
| 25 | Geelhoed;<br>2013       | System | <ul style="list-style-type: none"> <li>• Integration</li> <li>• Educational meetings</li> </ul>                                      | Integrated maternal child health and HIV care  | Usual Non-integrated care | <p>1) ART in labor: post intervention:112/121 (93%)</p> <p>2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%);</p> <p>3) Infants HIV-positive: post intervention: 9/123 (7%)</p>  | <p>1) ART in labor: intervention phase =93/96(97%)</p> <p>2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%)</p> <p>3) Infants HIV positive: intervention phase: 7/60(12%)</p>  | <p>1) 0.96 (0.90-1.02)</p> <p>2) 0.93 (0.88-0.97)</p> <p>3) 0.63 (0.25-1.60)</p>  | --  |
| 26 |                         |        |  |  |                           |   |  |   |   |
| 27 |                         |        |  |  |                           |   |  |   |   |
| 28 |                         |        |  |  |                           |   |  |   |   |
| 29 |                         |        |  |  |                           |   |  |   |   |
| 30 | Killam;<br>2010         | System | <ul style="list-style-type: none"> <li>• Integration</li> </ul>  | Integration of antenatal and HIV care  | Usual non-integrated care | ART initiation during pregnancy: 278/846 (32.9%)  | ART initiation during pregnancy: 103/716 (14.4%)   | 2.28 (1.86-2.80)  | AOR 2.01 (1.37, 2.95)   |
| 31 |                         |        |  |  |                           |   |  |   |   |
| 32 |                         |        |  |  |                           |   |  |   |   |
| 33 |                         |        |  |  |                           |   |  |   |   |
| 34 |                         |        |  |  |                           |   |  |   |   |
| 35 |                         |        |  |  |                           |   |  |   |   |
| 36 |                         |        |  |  |                           |   |  |   |   |
| 37 | Odeny ;<br>2014         | System | <ul style="list-style-type: none"> <li>• The use of information and communication technology</li> </ul>                              | SMS test messages during pregnancy and after delivery  | Usual care                | <p>1) Maternal postpartum clinic attendance: 38/194 (19.6%)</p> <p>2) Infant HIV testing by 8 wks: 1172/187 (92.0%)</p>   | <p>1) Maternal postpartum clinic attendance: 22/187 (11.8%)</p> <p>2) Infant HIV testing by 8 wks: 154/181 (85.1%)</p>   | <p>1) 1.66 (1.03-2.70)</p> <p>2) 1.08 (1.00-1.16)</p>   | --  |
| 38 |                         |        |  |  |                           |   |  |   |   |
| 39 |                         |        |  |  |                           |   |  |   |   |
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| 41 |                         |        |  |  |                           |   |  |   |   |
| 42 |                         |        |  |  |                           |   |  |   |   |
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| 49 |                         |        |  |  |                           |   |  |   |   |
| 50 |                         |        |  |  |                           |   |  |   |   |
| 51 |                         |        |  |  |                           |   |  |   |   |
| 52 |                         |        |  |  |                           |   |  |   |   |
| 53 |                         |        |  |  |                           |   |  |   |   |
| 54 | Rotheram-Borus;<br>2014 | System | <ul style="list-style-type: none"> <li>• Role expansion or task shifting</li> <li>• Outreach services</li> </ul>                     | Antenatal and postnatal home visits from community health workers                            | Usual care                | <p>1) ART prior to labor: 169/179 (94.4%)</p> <p>2) AZT or HAART during labor: 1164/179 (91.6%)</p> <p>3) NVP or HAART at onset of labor: 166/179 (92.7%)</p> <p>4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%)</p> <p>5) Infant ART after birth: 172/179 (96.1%)</p> <p>6) Infant HIV testing at 6 weeks: 155/160 (96.9%)</p> | <p>1) ART prior to labor: 149/159 (93.7%)</p> <p>2) AZT or HAART during labor: 147/159 (92.5%)</p> <p>3) NVP or HAART at onset of labor: 142/159 (89.3%)</p> <p>4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%)</p> <p>5) Infant ART after birth: 142/159 (89.3%)</p> <p>6) Infant HIV testing at 6 weeks: 132/140 (94.3%)</p> | <p>1) 1.01 (0.95-1.06)</p> <p>2) 0.99 (0.93-1.06)</p> <p>3) 1.04 (0.97-1.11)</p> <p>4) 1.08 (1.01-1.15)</p> <p>5) 1.08 (1.01-1.14)</p> <p>6) 1.03 (0.98-1.08)</p> | <p>1) AOR 1.08 (0.42, 2.80)</p> <p>2) AOR 0.87 (0.39, 1.95)</p> <p>3) AOR 1.52(0.70, 3.31)</p> <p>4) AOR 2.94(1.41, 6.12)</p> <p>5) AOR 2.95 (1.12, 7.73)</p> <p>6) AOR 1.80 (0.62, 5.28)</p> |
| 55 |                         |        |  |  |                           |   |  |   |   |
| 56 |                         |        |  |  |                           |   |  |   |   |
| 57 |                         |        |  |  |                           |   |  |   |   |
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|---------------|--------|----------------------------------|--|----------------------------|--|---|---|--|
| Rustagi; 2016 | System | • Continuous quality improvement | Facility level systems analysis and improvement intervention | No-intervention            | 1) ART in pregnancy: 575/839 (69%)<br>2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)   | 1) ART in pregnancy: 664/1037(64%)<br>2) Infant HIV tested by 6-8 wks: 270/710.6 (38%)  | 1) 1.07 (1.00-1.14)<br>2) 1.23 (1.09-1.40)  | --<br>--   |
| Turan; 2015   | System | • Integration                    | Integrated HIV and antenatal care                            | Usual, non-integrated care | 1) ART during pregnancy: 138/173 (80%)<br>2) ART during Labor: 28/173 (16%)<br>3) ART after birth: 22/173 (13%)<br>4) Infant ART after birth: 50/173 (29%)<br>5) ART throughout all 3 PMTCT periods: 37/176 (21.0%)<br>6) Infant HIV testing before 3 months: 143/569 (25%)<br>7) Infant HIV testing at 9 months: 361/569 (63%)<br>8) Infants HIV tested by 6 weeks: 143/568 (25%)<br>9) Infants HIV positive at 6 weeks: 16/143 (4.2%)<br>10) Infants HIV tested by end of study (up to 12 m): 382/568 (67.3%)<br>11) Infants HIV positive at 9 months: 28/382 (7.3%) | 1) ART during pregnancy: 75/152 (49%)<br>2) ART during Labor: 84/152 (55%)<br>3) ART after birth: 57/152 (38%)<br>4) Infant ART after birth: 106/152 (70%)<br>5) ART throughout all 3 PMTCT periods: 23/153 (15.0%)<br>6) Infant HIV testing before 3 months: 106/603 (18%)<br>7) Infant HIV testing at 9 months: 326/603 (54%)<br>8) Infants HIV tested by 6 weeks: 106/594 (18%)<br>9) Infants HIV positive at 6 weeks: 7/106 (6.6%)<br>10) Infants HIV tested by end of study (up to 12 m): 338/594 (57.0%)<br>11) Infants HIV positive at 9 months: 27/338 (8.0%) | 1) 1.61 (1.35-1.93)<br>2) 0.29 (0.20-0.42)<br>3) 0.34 (0.22-0.53)<br>4) 0.41 (0.32-0.54)<br>5) 1.40 (0.87-2.24)<br>6) 1.43 (1.14-1.79)<br>7) 1.17 (1.07-1.29)<br>8) 1.41 (1.13-1.76)<br>9) 0.64 (0.22-1.84)<br>10) 1.18 (1.08-1.29)<br>11) 0.92 (0.55-1.53) | 1) AOR 4.05 (2.0, 8.0)<br>2) AOR 0.16 (0.04, 0.68)<br>3) AOR 0.24 (0.08, 0.70)<br>4) AOR 0.18 (0.09, 0.35)<br>5) AOR 1.72 (0.85, 3.48)<br>6) AOR 1.57 (0.61,4.07)<br>7) AOR 1.47 (0.76,2.86)<br>8) AOR 1.57 (0.61-4.07)<br>9) AOR 0.62 (0.20,1.98)<br>10) AOR 1.45 (0.71,2.82)<br>11) AOR 0.89 (0.56,1.43) |

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302 Table 3: Results of Included Studies by PMTCT outcome

| PMTCT outcome        | Author/Year  | EPOC Category (s) | Intervention                        | Outcome Intervention group Number (%) | Outcome Control group Number (%) | Risk Ratio (95% CI) |
|----------------------|--------------|-------------------|-------------------------------------|---------------------------------------|----------------------------------|---------------------|
| ART use in pregnancy | Turan; 2015  | Integration       | Integration of ANC and HIV services | 138/173 (80%)                         | 75/152 (49%)                     | 1.61 (1.35-1.93)*   |
|                      | Killam; 2010 | Integration       | Integration of ANC and HIV services | 278/846 (32.9%)                       | 103/716 (14.4%)                  | 2.28 (1.86-2.80)*   |

|  |                       |   |   |                                    |                 |  |
|--|-----------------------|---|---|------------------------------------|-----------------|--|
|  |                       |   |   |                                    |                 |  |
|  | Ezeanolue; 2015       | Outreach Services   | Monthly church based "baby showers" including: educational games, delivery supply packs, lab testing and contact point for follow-up              | 24/41 (65%)                        | 12/32 (50%)     | 1.56 (0.93-2.62)*                          |
|  | Phiri: 2017           | Role expansion or task shifting outreach services:<br>The use of information and communication technology | Facility based peer support from mentor mothers arm<br><br>Community based peer support from mentor mothers arm                                   | 355/394 (90%)<br><br>366/428 (86%) | 361/447(81%)    | 1.06 (1.00-1.12),<br><br>1.12 (1.06-1.18)* |
|  | Aliyu; 2016           | Role expansion/task shifting<br>Integration:<br>Packages of care  | Integrated package of PMTCT services: point of care CD4 testing, decentralized PMTCT care, integrated mother/infant services, community champions | 166/172 (97%)                      | 77/197 (39%),   | 2.47 (2.07-2.95)*                          |
|  | Dryden-Peterson; 2015 | The use of information and communication technology:<br>Educational meetings                              | Staff training and support to ante-natal clinics, SMS transmission of HIV results to clinic staff   | 56/154 (36.4%)                     | 37/153 (24.2%)  | 1.50 (1.06-2.13)                           |
|  | Oyeledun; 2017        | Continuous Quality Improvement  | A quality improvement initiative  | 261/264 (98.9%)                    | 233/247 (94.3%) | 1.05 (1.01-1.08)                           |
|  | Rotheram-Borus; 2014  | Role expansion or task shifting:<br>Outreach services   | Ante- and post-natal home community   | 169/179 (94.4%)                    | 149/159 (93.7%) | 1.01 (0.95-1.06)                           |

|                                    |                      |   |   |                                      |                                    |                                      |
|------------------------------------|----------------------|---|---|--------------------------------------|------------------------------------|--------------------------------------|
|                                    |                      |   | health worker home visits   |                                      |                                    |                                      |
|                                    | Rustagi; 2016        | Continuous Quality Improvement                        | Facility level system analysis and improvement intervention                 | 575/839 (69%)                        | 664/1037(64%)                      | 1.07 (1.00-1.14)                     |
|                                    | Richter, 2014        | Role expansion or task shifting: Educational meetings | Peer led educational meetings   | 340/377 (90.2%)                      | 455/466 (95.5%)                    | 0.92 (0.89-0.96)**                   |
| <b>ART in Labor &amp; Delivery</b> | Kieffer; 2011        | Educational Meetings                                  | 1-day PMTCT knowledge and skills training for nurses and midwives           | 373/465(80%)                         | 325/472 (69%)                      | 1.17 (1.08-1.26)*                    |
|                                    | Weiss; 2014          | Group (couple) vs. individual care                    | Couples based HIV/PMTCT counseling  | 9/12 (75%)                           | 16/12 (50%)                        | 1.50 (0.78-2.88)                     |
|                                    | Richter, 2014        | Role expansion or task shifting: Educational meetings | Peer led education meetings   | 282/377 (74.8%);<br>361/377 (95.8%)  | 334/466(71.7%);<br>456/466 (97.9%) | 1.04 (0.96-1.13); 0.98 (0.95-1.00)   |
|                                    | Geelhoed; 2013       | Integration: Educational meetings                     | Integration of maternal/child health and HIV services ante- and post-partum | 112/121 (93%)                        | 93/96(97%)                         | 0.96 (0.90-1.02)                     |
|                                    | Rotheram-Borus; 2014 | Role expansion or task shifting: Outreach services    | Ante- and post-natal home community health worker home visits               | 1164/179 (91.6%);<br>166/179 (92.7%) | 147/159 (92.5%)<br>142/159 (89.3%) | 0.99 (0.93-1.06)<br>1.04 (0.97-1.11) |
|                                    | Turan; 2015          | Integration   | Integration of ANC and HIV services   | 28/173 (16%)                         | 84/152 (55%)                       | 0.29 (0.20-0.42)**                   |
| <b>ART in post-</b>                | Turan; 2015          |   | Integration of ANC and HIV services   | 22/173 (13%)                         | 57/152 (38%)                       | 0.34 (0.22-0.53)**                   |

| partum period                           |                      |   |   |                                     |                                  |                                    |
|---|----------------------|---|---|-------------------------------------|----------------------------------|------------------------------------|
| <b>ART across the PMTCT cascade</b>     | Yotebieng; 2016      | Conditional Cash Transfers                            | Conditional cash transfers  | 146/216 (67.6%)                     | 116/217 (53.5%)                  | 1.26 (1.08-1.48)*                  |
|   | Turan; 2015          | Integration   | Integration of ANC and HIV services   | 37/176 (21.0%)                      | 23/153 (15.0%)                   | 1.40 (0.87-2.24)                   |
| <b>Infant Prophylaxis at birth</b>      | Rotheram-Borus; 2014 | Role expansion or task shifting: Outreach services    | Ante- and post-natal home community health worker home visits               | 171/179 (95.5%)                     | 141/159 (88.7%)                  | 1.08 (1.01-1.14)*                  |
|   | Reynolds; 2010       | Self Management: Educational Outreach                 | Take home infant prophylaxis  | 80/85 (94%)                         | 66/75 (88%)                      | 1.07 (0.97-1.18)                   |
|   | Richter, 2014        | Role expansion or task shifting: Educational meetings | Peer led educational meetings   | 364/377 (96.6%);<br>348/377 (92.3%) | 451/466(96.8%);<br>374/466 (80%) | 1.00 (0.97-1.02); 1.15 (1.09-1.21) |
|   | Oyeledun; 2017       | Continuous Quality Improvement                        | Quality Improvement intervention  | 138/209 (66%)                       | 145/194 (74.7%)                  | 0.88 (0.78-1.00)                   |
|   | Geelhoed; 2013       | Integration: Educational meetings                     | Integration of maternal/child health and HIV services ante- and post-partum | 117/126 (93%)                       | 95/95(100%)                      | 0.93 (0.88-0.97)                   |
|   | Turan; 2015          | Integration   | Integration of ANC and HIV services   | 50/173 (29%)                        | 106/152 (70%)                    | 0.41 (0.32-0.54)**                 |
| <b>Infant HIV testing at 6-10 weeks</b> | Oyeledun; 2017       | Continuous Quality Improvement                        | Quality improvement intervention  | 102/209 (48.8%)                     | 49/194 (25.3%)                   | 1.93 (1.46-2.55)*                  |



|                                       |                      |  |   |                              |                 |                                       |
|---------------------------------------|----------------------|--|---|------------------------------|-----------------|---------------------------------------|
|                                       | Tomlinson; 2014      | Role expansion or task shifting: Outreach services   | Increased training of and home visits by community health workers                 | 420/571(73.6%)               | 465/698(66.6%)  | 1.10 (1.03-1.19)*                     |
|                                       | Odeny; 2014          | The use of information and communication technology  | Ante- and Post-natal SMS texts to patients  | 1172/187 (92.0%)             | 154/181 (85.1%) | 1.08 (1.00-1.16)*                     |
|                                       | Turan; 2015          | Integration  | Integration of ANC and HIV services   | 143/568 (25%)                | 106/594 (18%)   | 1.41 (1.13-1.76)                      |
|                                       | Rotheram-Borus; 2014 | Role expansion or task shifting: Outreach services   | Ante- and post-natal home community health worker home visits                     | 155/160 (96.9%)              | 132/140 (94.3%) | 1.03 (0.98-1.08)                      |
|                                       | Rustagi; 2016        | Continuous Quality Improvement   | Facility level system analysis and quality improvement intervention               | 283/604.4 (47%)              | 270/710.6 (38%) | 1.23 (1.09-1.40)                      |
|                                       | Phiri; 2017          | Role expansion or task shifting outreach services: The use of information and communication technology | Facility level peer mentor support arm<br>Community based peer mentor support arm | 200/289(69%)<br>95/286 (68%) | 169/273(62%)    | 1.12 (0.99-1.26)<br>1.23 (1.11-1.38)* |
| <b>Infant HIV Positive at 6 weeks</b> | Turan; 2015          | Integration  | Integration of ANC and HIV services   | 16/143 (4.2%)                | 7/106 (6.6%)    | 0.64 (0.22-1.84)                      |
|                                       | Weiss; 2014          | Group (couple) vs. individual care   | Couples based HIV/PMTCT counseling  | 1/30 (3.3%)                  | 3/39 (7.7%)     | 0.43 (0.05-3.96)                      |
|                                       | Yotebieng; 2016      | Conditional Cash Transfers   | Conditional cash transfers  | 5/169 (3.0%)                 | 6/156 (3.9%)    | 0.77(0.24-2.47)                       |

|                                       |                 |  |   |  |                   |  |
|---------------------------------------|-----------------|--|---|--|-------------------|--|
|                                       | Phiri; 2017     | Role expansion or task shifting outreach services: The use of information and communication technology | Facility level peer mentor support arm<br><br>Community based peer mentor support arm   | 1/199(1%)<br><br>2/195 (2%)  | 2/169(1%)         | 0.42 (0.04-4.64)<br><br>0.87 (0.12-6.09) |
| <b>Retention in care at 6-8 weeks</b> | Yotebieng; 2016 | Conditional Cash Transfers   | Conditional cash transfers  | 174/216 (80.6%)  | 157/217 (72.4%)   | 1.11 (1.00-1.23)*                        |
|                                       | Aliyu; 2016     | Role expansion/task shifting<br>Integration:<br>Packages of care                                       | Integrated package of PMTCT services: point of care CD4 testing, decentralized PMTCT care, integrated mother/infant services, community champions | 125/150 (83%)  | 15/170 (9%)       | 9.44 (5.60-15.4)*                        |
|                                       | Ezeanolue; 2015 | Outreach Services  | Monthly church based "baby showers" including: educational games, delivery supply packs, lab testing and contact point for follow-up              | 33/41(81%)   | 28/32(88%)        | 0.92 (0.75-1.12)                         |
| <b>Retention in care at 12 months</b> | Mwapasa; 2017   | Integration: The use of information and communication technology                                       | Integration of ANC and HIV care and routine patient tracing arm   | 89/461 (19.3%) M   | 90/396(22.7%)M    | 0.85(0.65-1.10)M                         |
|                                       |                 |  |   | 334/461(72.4%)M  | 274/396(69.1%)M   | 1.05(0.96-1.14)M                         |
|                                       |                 |  |   | 32/386 (8.3%) I  | 32/300 (10.7 %) I | 0.78 (0.49-1.24)I                        |
|                                       |                 |  |   | 291/386 (75.4%) I  | 234/300 (78.0%) I | 0.97 (0.89-1.05) I                       |
|                                       |                 |  |   | 115/493(23.3%) M   | 332/493 (67%) M   | 1.03(0.81-1.31)M                         |
|                                       |                 |  |   | Integration of ANC and HIV care and SMS enhanced patient tracing arm | 82/399 (20.1%) I  | 1.03(0.81-1.31)M                         |
|                                       |                 |  |   | 323/399 (80.9%) I  |                   | 0.97(0.89-1.06)M                         |
|                                       |                 |  |   |  |                   | 1.93 (1.32-2.82) I                       |
|                                       |                 |  |   |  |                   | 1.04(0.96-1.12) I                        |

|                                       |             |   |   |   |                                   |   |
|---------------------------------------|-------------|---|---|---|-----------------------------------|---|
|                                       |             |   |   |   |                                   |   |
|                                       | Phiri: 2017 | Role expansion or task shifting outreach services:<br>The use of information and communication technology | Facility level peer mentor support arm<br><br>Community based peer mentor support arm | 277/366 (78%)<br><br>258/355(74%)                                   | 261/361 (74%)                     | 1.05(0.96-1.14)<br><br>1.01 (0.92-1.10)*  |
| <b>Retention in care at 24 months</b> | Phiri: 2017 | Role expansion or task shifting outreach services:<br>The use of information and communication technology | Facility level peer mentor support arm<br><br>Community based peer mentor support arm | 223/428(52%)<br>298/428 (70%)<br><br>211/394 (54%)<br>292/394 (74%) | 169/447 (38%)<br><br>255/447(57%) | 1.38(1.19-1.60)<br><br>1.22(1.10-1.35)*<br><br>1.42 (1.22-1.65)*<br><br>1.30 (1.18-1.43)* |

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305 Findings of the narrative synthesis are outlined below first as intervention types within  
306 intervention target categories (patient, provider, system) and then by PMTCT outcome.

307 Descriptive synthesis of findings according to intervention target level(s):

308 Findings according to level of intervention are outlined in table 2.

309 Patient Level Interventions:

310 Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of  
311 bias ranged from 3 to 6 of 6 criteria rated as high or unclear. Ezeanolue et al. (27) included 40  
312 clusters and 3,024 patients and evaluated a complex intervention that included monthly baby  
313 showers at participating churches where expectant mothers participated in educational games,  
314 received ‘mama packs’ containing supplies needed during delivery (sterile gloves, alcohol  
315 swabs, clean razor, etc.) and laboratory testing, and were given a contact point for follow-up.

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3 316 Women in the intervention group were found to be significantly more likely to complete linkage  
4  
5 317 to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI  
6  
7 318 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks  
8  
9  
10 319 postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided  
11  
12 320 pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at  
13  
14 321 home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss  
15  
16 322 et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT  
17  
18 323 intervention compared to standard care. They found no statistically significant difference in  
19  
20 324 PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant  
21  
22 325 blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and  
23  
24 326 evaluated whether conditional cash transfers improved adherence, acceptance of and retention in  
25  
26 327 PMTCT services to 6 weeks postpartum. They found women in the intervention group were  
27  
28 328 significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have  
29  
30 329 attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95%  
31  
32 330 CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.  
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#### 40 Patient/Provider Level Interventions:

41  
42 333 One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention  
43  
44 334 directed at both patients and providers in which peer mentors were trained to provide in person  
45  
46 335 education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31).  
47  
48 336 They found patients in the intervention group were significantly less likely to adhere to ARTs  
49  
50 337 during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [95% CI 0.26-  
51  
52 338 0.74]). No statistically significant effects were found on the remaining outcomes including: ART  
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3 339 use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART  
4  
5 340 post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were  
6  
7 341 unable to reach authors for additional information on long term outcomes.  
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12 343 Provider Level Interventions:  
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14 344 Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day  
15  
16 345 PMTCT knowledge and skills training course for nurses and midwives compared to standard  
17  
18 346 training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They  
19  
20 347 found a statistically significant increase in the proportion of women with ART detected in cord  
21  
22 348 blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).  
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28 350 Provider/System Level Interventions:  
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31 351 Five studies reported interventions directed at both the provider and health system level  
32  
33 352 (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-  
34  
35 353 Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated  
36  
37 354 transmission of HIV test results to clinic staff via short message service (SMS), and ongoing  
38  
39 355 support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring  
40  
41 356 and addressing clinic underperformance). There was a trend towards an increase in the  
42  
43 357 proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.  
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48  
49 359 Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess  
50  
51 360 the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing  
52  
53 361 (MIP+SMS) combined with integrated care against standard care (SOC). They found no  
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3 362 significant difference in maternal retention in care at 12 months in either intervention group  
4  
5 363 relative to controls using study definitions, or ministry of health definitions for retention. They  
6  
7  
8 364 found no statistically significant difference in infant retention in care at 12 months in either  
9  
10 365 intervention group relative to controls using study definitions, or ministry of health definitions  
11  
12 366 for retention .  
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15 367  
16  
17 368 Oyeledun et al. (35) compared a continuous quality improvement intervention including  
18  
19 369 coaching visits and collaborative meetings to standard ministry of health support in 32 clusters  
20  
21 370 and 511 patients. They found no significant difference in retention in care at 6 months, in  
22  
23 371 initiation of ART prophylaxis in infants within 72 hours of birth, or in proportion of women  
24  
25 372 initiated on ARTs within 2 weeks of enrolment. They found significantly improved rates of  
26  
27 373 infant HIV testing at 6-10 weeks (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-  
28  
29 374 2.42]).  
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33 375  
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35 376 Phiri et al. (36) conducted a 3-arm cluster RCT with 21 clusters and 1269 women evaluating  
36  
37 377 facility-based peer support (FBPS) and community-based peer support (CBPS) from expert  
38  
39 378 mothers against standard of care (SOC). They found non-significant improvement with FBPS  
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41  
42 379 and small statistically significant improvements with CBPS in uptake of ARTs (RR= 1.12 [95%  
43  
44 380 CI 1.06-1.18]; ARD 0.09 [95% CI 0.01-0.18]), retention in care at 1 year (RR=1.01 [95% CI  
45  
46 381 0.92-1.10]; ARD= 0.08 [95% CI 0.04-0.20]), and retention in care at 2 years (RR= 1.42 [95% CI  
47  
48 382 1.22-1.65]; ARD=0.16 [95% CI 0.03-0.30]), relative to SOC. Retention in care at 2 years was  
49  
50 383 significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-  
51  
52 384 1.43]) using ministry of health definitions for retention in care. Infant HIV testing at 6 weeks was  
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3 385 significantly higher in the CBPS only (RR=1.23 [95% CI 1.11-1.38]). There was no difference in  
4  
5 386 infant HIV positive rates at 6 weeks in either intervention group.  
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8 387  
9  
10 388 Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased  
11  
12 389 training of community health workers and increased home visits by community health workers  
13  
14 390 during and post delivery to provide PMTCT counselling and newborn care. They found a  
15  
16 391 significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention  
17  
18 392 group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in  
19  
20 393 mother to child HIV transmission at 12 weeks.  
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26 395 System Level Interventions:  
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28 396 Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias  
29  
30 397 ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or  
31  
32 398 unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services  
33  
34 399 including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and  
35  
36 400 community involvement through male champions, compared to standard care across 12 clusters  
37  
38 401 and 369 patients. They found significant improvement in the proportion of eligible women  
39  
40 402 started on ART for PMTCT (RR= 2.47 [95% CI 2.07-2.95]; ARR 3.3 [95% CI 1.4-7.8]), and in  
41  
42 403 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI  
43  
44 404 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-  
45  
46 405 19.7]).  
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3 407 Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and  
4  
5 408 evaluated the impact of integration of HIV and maternal child health services during both  
6  
7 409 antenatal and postnatal periods. They found no improvement in the proportion of women  
8  
9 410 receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48  
10  
11 411 hours and the proportion of HIV positive infants.  
12  
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14 412  
15  
16 413 Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual  
17  
18 414 care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a  
19  
20 415 statistically significant increase in the proportion of eligible women receiving ARTs during  
21  
22 416 pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).  
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28 418 Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during  
29  
30 419 pregnancy and post-delivery. They found statistically significant improvements in maternal  
31  
32 420 antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks  
33  
34 421 (RR= 1.08 [1.00-1.16]).  
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40 423 Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in  
41  
42 424 addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in  
43  
44 425 the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14];  
45  
46 426 AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the  
47  
48 427 intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no  
49  
50 428 significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal  
51  
52 429 NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.  
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430  
431 Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters  
432 in 3 countries, including 1876 patients. They found no significant improvement in the proportion  
433 of pregnant women receiving ARTs (RR= 1.07 [95% CI 1.00- 1.14]) or infants tested for HIV by  
434 6-8 weeks (RR= 1.23 [95% CI 1.09-1.40]).

435  
436 Turan et al. (25) included 12 clusters and 1172 patients and examined the effects of integration  
437 of HIV and antenatal care compared with standard non-integrated care. Self-reported maternal  
438 ART use across the PMTCT spectrum, pre, during, and post delivery, was not significantly  
439 different between groups, although it was significantly higher during pregnancy (RR=  
440 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]). ART use was significantly lower among  
441 intervention sites during labor and delivery RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI  
442 0.04, 0.68] and post-delivery (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]). Infant  
443 ART use after birth was significantly lower in intervention sites (RR= 0.41 [95% CI 0.32-0.54];  
444 AOR= 0.18 [95% CI 0.09-0.35]), although infant HIV testing was increased at 6 weeks, and 9  
445 months in intervention sites, the difference was not statistically significant. No difference was  
446 found for infant HIV infection rates at 6 weeks, or 9 months.

447  
448 Descriptive synthesis of findings according to PMTCT outcomes:

449 Findings according to PMTCT outcome are outlined in table 3. The vast majority of studies  
450 reported short-term PMTCT outcomes with ART use during pregnancy (10/18) and labor and  
451 delivery (6/18), infant prophylaxis at birth (6/18), and infant HIV testing at 6-10 weeks (5/18).

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3 452 Overall, findings are often mixed and effect sizes small, with many of uncertain clinical  
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5 453 significance.  
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10 455 Five studies found significant improvements in ART use during pregnancy ranging with RR  
11  
12 456 ranging from 1.12 to 2.48 (25, 26, 27, 36, 38). Effective interventions included: integration of  
13  
14 457 ANC and HIV services (RR= 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]) (25) and (RR=  
15  
16 458 2.28 [95% CI 1.86-2.80] AOR= 2.01 [95% CI 1.37-2.95]) (26); monthly baby showers at  
17  
18 459 participating churches providing education through games, ‘mama packs’ containing delivery  
19  
20 460 supplies, laboratory testing, and a contact point for follow-up (RR 1.56 [95% CI 0.93-2.62],  
21  
22 461 AOR=2.8 [95% CI 1.02-4.79]) (27); community based peer support from mentor mothers (RR=  
23  
24 462 1.12 [95% CI 1.06-1.18], ARR 0.09 [95% CI 0.01-0.18]) (36) ; and an integrated package of  
25  
26 463 PMTCT services including point-of-care CD4 testing, decentralized PMTCT care, integrated  
27  
28 464 mother/infant services, and community champions, (RR= 2.47 [95% CI 2.07-2.95], ARR 3.3  
29  
30 465 [95% CI 1.4-7.8]) (38). Four studies evaluating: staff training and support to ante-natal clinics,  
31  
32 466 and automated SMS transmission of HIV test results to clinic staff (33); a quality improvement  
33  
34 467 initiative (35); community health worker ante- and post-natal home visits (41); and facility level  
35  
36 468 systems analysis and improvement intervention (42), found no significant difference in ART use  
37  
38 469 during pregnancy. One study evaluating peer mentor led educational meetings, found ART  
39  
40 470 adherence during pregnancy lower in the intervention group (31).  
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47 471  
48  
49 472 Six studies reported ART use during labor and delivery, with 4/6 finding no significant effect  
50  
51 473 (29, 31, 39, 41)), 1 finding a significant but small improvement RR=1.17 (32) and 1 finding  
52  
53 474 significantly reduced ART use in the intervention group RR=1.614 (25). The one study that  
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3 475 found a small significant effect employed a 1-day PMTCT knowledge and skills training course  
4  
5 476 for nurses and midwives (RR= 1.17 [95% CI 1.08-1.26]) (32). Ineffective interventions included;  
6  
7 477 couples based PMTCT intervention (29), peer mentor led educational meetings (31), integration  
8  
9 478 of maternal child health and HIV services (39), and community health worker ante-natal and  
10  
11 479 post-partum home visits (41). In contrast to the findings for ART use during pregnancy, ART  
12  
13 480 use during labor and delivery was low significantly lower with integration of ANC and HIV care  
14  
15 481 RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI 0.04, 0.68] (25).

16  
17 482 Only 1 study evaluated ART use in the post-partum period and found significantly reduced ART  
18  
19 483 use during this period (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]) with integration of  
20  
21 484 ANC and HIV care (25). Two additional studies evaluated uptake across the cascade, with  
22  
23 485 conditional cash transfer found to significantly improve uptake of PMTCT recommendations  
24  
25 486 (RR= 1.26 [95% CI 1.08-1.48]) (30) and no difference found for integration of ANC and HIV  
26  
27 487 services (25).

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29 488  
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31 489 Six studies evaluated infant HIV prophylaxis at birth. One of 6 studies reported a small  
32  
33 490 significant improvement in infant HIV prophylaxis at birth with community health worker home  
34  
35 491 visits (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) ( 41), 1/6 significantly  
36  
37 492 reduced infant prophylaxis at birth with integration of ANC and HIV care (RR= 0.41 [95% CI  
38  
39 493 0.32-0.54]; AOR= 0.18 [95% CI 0.09-0.35]) (25) and 4/6 studies finding no significant  
40  
41 494 difference with take home nevirapine dosing (28), peer mentor led educational meetings (31), a  
42  
43 495 quality improvement intervention (35), and integration of maternal child health and HIV services  
44  
45 496 during both the ante-natal and postpartum periods (39).

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3 498 Seven studies reported infant HIV testing at 6-10 weeks. Three of 7 found significantly improved  
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5 499 rates of infant testing by 6-10 weeks of age with RR ranging from 1.08 to 1.93 (35,37,40), 3/7  
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7  
8 500 no difference (25, 41,42), and one study finding a mixed effect of peer support (36).  
9  
10 501 Improvements in infant HIV testing were found for a quality improvement intervention  
11  
12 502 (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-2.42]) (35), increased training of and  
13  
14 503 home visits from community health workers (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI  
15  
16 504 0.97-1.25]) (37), and SMS texts to patients both antenatally and post-delivery (RR= 1.08 [1.00-  
17  
18 505 1.16]) (40). One study found mixed effects of peer support on infant HIV testing, with  
19  
20  
21 506 community based peer support found to significantly improve infant HIV testing at 6 weeks  
22  
23 507 (RR=1.23 [95% CI 1.11-1.38]) and no difference found for facility based peer support (36). No  
24  
25 508 difference was found for integration of ANC and HIV care (25), home visits from community  
26  
27 509 health workers (41) or a facility level system analysis and quality improvement intervention (42).  
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30 510  
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32  
33 511 Outcome definitions for retention in care and infant HIV-positive rates were highly variable,  
34  
35 512 ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other  
36  
37 513 PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for  
38  
39 514 retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant  
40  
41 515 retention in care at 6 weeks, with 2 studies evaluating conditional cash transfers (30) and an  
42  
43 516 integrated package of PMTCT services including point-of-care CD4 testing, decentralized care,  
44  
45 517 integrated mother/infant services, and community champions (38), finding significantly  
46  
47 518 improved retention (RR= 1.11 [95% CI 1.00-1.23]) and (RR= 9.44 [95% CI 5.60-15.4];  
48  
49 519 ARR=9.1 [95% CI 5.2-15.9]) at 6 weeks, and a third employing monthly baby showers finding  
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52 520 no difference (27). Two studies examined retention in care at 1 year. One study evaluating  
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3 521 integration of ANC and HIV care with and without SMS enhanced tracing in a 3 arm trial and  
4  
5 522 found no difference in maternal or infant retention at 1 year (34). A second study evaluated the  
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7 523 effect of community based peer support (CBPS) and facility based peer support (FBPS) on  
8  
9 524 retention in care at 1 and 2 years, in a 3 arm trial. They found non-significant improvement with  
10  
11 525 FBPS and small statistically significant improvements with CBPS in retention in care at 1 year  
12  
13 526 (RR=1.01 [95% CI 0.92-1.10]) and 2 years (RR= 1.42 [95% CI 1.22-1.65]) using trial data (36).  
14  
15 527 Retention in care at 2 years was significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and  
16  
17 528 CBPS (RR= 1.30 [95% CI 1.18-1.43]) using ministry of health definitions for retention in care.  
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24 530 Four studies examined infant HIV-positive rates at 6-10 weeks post-partum. Evaluated  
25  
26 531 interventions included; integration of ANC and HIV care (25), couples based HIV/PMTCT  
27  
28 532 counselling (29), conditional cash transfers (30), and peer support (36). All found no difference.  
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### 33 534 **Discussion:**

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35 535 Eighteen studies were included in our review. Heterogeneity of interventions and outcome  
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37 536 reported limited both comparison across studies and intervention categories, as well as,  
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39 537 opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias,  
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41 538 primarily due to limitations inherent to health systems research and unclear reporting of key  
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43 539 methodological factors.  
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49 541 Based on our review findings, several interventions appear promising. In the single meta-  
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51 542 analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use  
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53 543 during pregnancy with integration of HIV and antenatal care compared to standard non-  
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3 544 integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies  
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5 545 found small positive effects of integration of HIV and antenatal care, alone or as part of a  
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8 546 complex intervention, on ART use during pregnancy. However, the effects of integration on  
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10 547 PMTCT outcomes during labor and delivery, and post-delivery were less clear, with no  
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12 548 difference found for some studies (39, 34) and for some outcomes (25), and one study finding  
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14 549 reduced ART use during labor and delivery, and post-delivery (25). While the findings of Turan  
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16  
17 550 et al. (25) occurred in the setting of resource challenges impacting implementation and relatively  
18  
19 551 low numbers of adherence reports beyond the antenatal period, this was the case for both  
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21 552 intervention and control groups. Therefore, as integrated care is now common practice future  
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23 553 work focusing on how integration of maternal child health and HIV care may be optimized alone  
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26 554 or in combination with other interventions to optimize PMTCT outcomes beyond the antenatal  
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28 555 period is needed.

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31 556  
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33 557 Four studies evaluating different approaches to outreach services alone or in combination with  
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35 558 other interventions found small positive effects on linkage to care, ART use during pregnancy  
36  
37 559 and labor/delivery, and early infant HIV testing. Two studies found positive effects of role  
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39 560 expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy  
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41 561 and, when combined with outreach services, positive effects were seen on long term retention in  
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43 562 care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT  
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45 563 outcomes, each in a single study, included: educational meetings, conditional cash transfers,  
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47 564 continuous quality improvement, and use of information and communication technology.  
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3 566 An important finding of the present review is the high degree of variability in outcome  
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5 567 definitions and relative lack of longer-term outcome data. While in some instances variability of  
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7 568 outcome definitions may be considered a strength where both self-report and biological markers  
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9 569 of ART use are included, variability in timing of outcomes limits comparison across studies and  
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11 570 opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the  
12  
13 571 findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is  
14  
15 572 clearly critical to reducing HIV transmission, longer term outcomes are equally important to  
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17 573 understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of  
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19 574 future work would be substantially improved through both standardization of timing of PMTCT  
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21 575 outcomes and through funding opportunities that would allow for evaluation of longer term  
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23 576 outcomes.  
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31 578 In keeping with other systematic reviews focused on interventions aimed at improving PMTCT  
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33 579 care and outcomes published to date (8,9,13,14,15), our review found the evidence base available  
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35 580 to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor  
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37 581 Car et al. (9), which included a single study and found improved ART use in labor/delivery from  
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39 582 integration of care, our single meta-analysis including 2 studies found a positive effect of  
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41 583 integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only  
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43 584 2 of which met inclusion criteria for the present review, and they also found variable effects of  
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45 585 non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al.  
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47 586 (14) included 10 articles, with 2 overlapping studies included in our review, and focused on  
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49 587 postpartum retention of women in PMTCT and ART care. This latter review, which included  
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51 588 both high and LMICs and a broader range of study designs, focused on a limited portion of the  
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3 589 PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone  
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5 590 interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to  
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7 591 improve PMTCT service delivery and promote retention. Their review was conducted over a  
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10 592 similar timeframe to the present review, however, it differs from the present review in its  
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12 593 inclusion of high income country studies, inclusion of a range of study designs, and in its  
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14 594 approach to categorization of interventions. Thirty-four studies were included in their review, 11  
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17 595 of which were included in the present review. They found weak evidence for improvement of  
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19 596 early infant HIV diagnosis from mobile-phone based interventions and for male involvement in  
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21 597 reducing infant HIV transmission.  
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26 599 Given the focus of the present review on providing evidence-based guidance to PMTCT program  
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28 600 planners and implementers based LMICs our review differs from the reviews noted above in  
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30 601 several ways. First, to optimize the quality of evidence we limited our review to randomized and  
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32 602 non-randomized controlled trials and interrupted times series studies. Second, to increase the  
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34 603 applicability of findings to LMIC implementers, we limited our review to studies conducted in  
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36 604 LMICs. Third, we included a broad range of intervention categories and included both maternal  
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38 605 and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to  
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40 606 provide information of direct relevance to implementation planning, we categorized and  
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42 607 analyzed interventions at both the level at which they are implemented (patient, provider,  
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44 608 system) and using the EPOC intervention classification scheme, which groups interventions  
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46 609 based on the intervention process/activities employed.  
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51 610 Limitations:  
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3 611 While agreement on data extraction was not calculated, an initial calibration exercise was carried  
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5 612 out to ensure consistency in data extraction. Following this, comparison of completed data  
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7 613 extraction forms revealed few differences. Although no study was excluded for language, it is  
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9 614 possible that use of translation software may have resulted in exclusion of an eligible study due  
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11 615 to inaccurate translation. Additionally, while unlikely to have led to a significant difference in  
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13 616 results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO  
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15 617 as the later was not accessible to the second information technologist.  
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21 619 The multifaceted nature of the majority of interventions evaluated and variability in PMTCT  
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23 620 outcomes reported, limited our ability to combine studies statistically and to separate  
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25 621 effective/ineffective features of the interventions. In addition, efforts to contact authors for data  
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27 622 necessary for risk ratio calculations was ineffective in several cases. Due to the small number of  
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29 623 studies included in the meta-analysis publication bias could not be examined. Additionally,  
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31 624 although pre-specified in our protocol, interpretation of findings, most commonly infant HIV  
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33 625 infection rates, are limited by lack of power to assess secondary outcomes among included  
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35 626 studies. As 7 of the 18 studies limited participation to women 17-18 years of age or older, results  
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37 627 may be less generalizable to younger mothers. Finally, although the EPOC search filter is  
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39 628 designed to identify articles from all low- and middle-income countries, only articles from Sub-  
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41 629 Saharan Africa were included in the review. Results therefore may be less generalizable to  
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43 630 LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the  
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45 631 evidence to date and where funding should be targeted for future research based on knowledge  
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47 632 users needs.  
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3 634 *Future Directions:*  
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5 635 Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were  
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7 636 generally small and often mixed across studies, and based on a small number of studies that were  
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10 637 largely at moderate to high risk of bias. Further research is needed both to improve quantity and  
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12 638 quality of data. First, replication of promising approaches is needed. Second, improved  
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14 639 publication reporting to ensure key methodological factors are addressed and to provide detail on  
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16 640 the likely impact of factors that cannot be modified through design. This transparency in  
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18 641 reporting will enhance interpretation and utility of findings in informing PMTCT policy and  
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20 642 program decision making. For example, while the nature of designs for evaluating PMTCT  
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22 643 interventions, often make blinding of participants impossible, description of the context and  
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24 644 likely impact would aid interpretation. Additionally, use of blinded outcome assessment or  
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26 645 objective outcomes such as laboratory confirmation of ART in blood samples will increase study  
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28 646 impact. Third, given the inherent difficulties in evaluating complex interventions, increased use  
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30 647 of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would  
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32 648 be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade and  
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34 649 longer term outcomes in particular where feasible, would allow for increased comparison across  
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36 650 interventions.  
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45 652 **Conclusions:**

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47 653 The body of evidence synthesized in this review and in the literature to date on effectiveness of  
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49 654 interventions to improve uptake and retention of mothers and infants in PMTCT care is limited  
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51 655 by low quality evidence. A single meta-analysis of 2 studies employing integration of antenatal  
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53 656 and HIV care suggested a potential for improvement of ART use during pregnancy based on  
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3 657 weak evidence. Overall findings are mixed and effect sizes small and of uncertain clinical  
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5 658 significance. In order to improve the utility of evidence to program planners future studies  
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7 659 should strive to include key outcomes across the range of the PMTCT cascade where feasible,  
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9 660 reduce risk of bias where possible and improve reporting of key methodological factors to allow  
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11 661 for improved assessment of risk of bias and understanding of the likely impact of risk of bias  
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13 662 where it cannot be addressed in design.  
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19 664 **List of abbreviations:** ANC: Antenatal care; ART: Anti-Retroviral Therapy; AZT: Zidovudine,  
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21 665 EPOC: Effective Practice and Organization of Care; HAART: Highly active antiretroviral  
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23 666 therapy, HIV: Human Immunodeficiency Virus; LMIC: Low and Middle Income Country;  
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25 667 MeSH: Medical Subject Headings; MOH: Ministry of Health; NVP: Nevirapine, PMTCT:  
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27 668 Prevention of mother to child transmission of HIV; RCT: Randomized controlled trial; SMS:  
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29 669 Short message service; SOC: Standard care; Versus: vs.  
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35 671 **Declarations:**

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37 672 **Ethics approval and consent to participate:** Not applicable.

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39 673 **Consent for publications:** Not applicable.

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41 674 **Availability of data and material:** No additional data available.

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51 679 Diseases (P30 AI50410 and R01 AI131060-01).  
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3 680 **Competing Interests:** The authors have declared that no competing interests exist. The authors  
4  
5 681 alone are responsible for the writing and content of the paper.  
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8 682  
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10 683 **Authors' contributions:** LPR and MvL conceived the study. LPR and SS developed the search  
11  
12 684 strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of  
13  
14 685 article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence  
15  
16 686 tables and manuscript. LPR conducted the meta-analysis with support from BP, MCH, NER, SP,  
17  
18 687 ML, and FC provided content expertise and assisted with preparation of the protocol and  
19  
20 688 manuscript. All authors provided critical revision of the manuscript and read and approved the  
21  
22 689 final manuscript.  
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49 831  
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53 833 intervention on retention-in-care at 6 months postpartum in a PMTCT program in northern

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3 834 Nigeria: Results of a cluster randomized controlled study. *J Acquir Immune Defic Syndr.*  
4  
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12 838 models on maternal uptake and retention in Malawi's option B+ HIV prevention of mother-to-  
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19 841  
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23 843 of an integrated, community-based package for maternal and newborn care, with prevention of  
24  
25 844 mother-to-child transmission of HIV in a South African township. *Trop Med Int Health.*  
26  
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31 846  
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33 847 38- Aliyu MH, Blevins M, Audet CM, et al. Integrated prevention of mother-to-child HIV  
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35 848 transmission services, antiretroviral therapy initiation, and maternal and infant retention in care  
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37 849 in rural north-central Nigeria: A cluster-randomised controlled trial. *Lancet HIV.* 2016;3:e202-  
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39 850 11.  
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42 851  
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44 852 39- Geelhoed D, Lafort Y, Chissale É, et al. Integrated maternal and child health services in  
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46 853 Mozambique: Structural health system limitations overshadow its effect on follow-up of HIV-  
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48 854 exposed infants. *BMC Health Serv Res.* 2013;13:207.  
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3 856 40- Odeny TA, Bukusi EA, Cohen CR, et al. Texting improves testing: A randomized trial of  
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5 857 two-way SMS to increase postpartum prevention of mother-to-child transmission retention and  
6  
7 858 infant HIV testing. *AIDS*. 2014;28:2307-2312.  
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10 859  
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12 860 41- Rotheram-Borus MJ, Tomlinson M, Le Roux IM, et al. A cluster randomised controlled  
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14 861 effectiveness trial evaluating perinatal home visiting among South African mothers/infants. *PLoS*  
15  
16 862 *ONE*. 2014;9:e105934.  
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19 863  
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21 864 42- Rustagi AS, Gimbel S, Nduati R, et al. Implementation and operational research: Impact of a  
22  
23 865 systems engineering intervention on PMTCT service delivery in Cote d'Ivoire, Kenya,  
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25 866 Mozambique: A cluster randomized trial. *J Acquir Immune Defic Syndr*. 2016;72:e68-76.  
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30  
31 868 **Captions for appended Tables and Figures:**

32  
33 869 Table 1: Characteristics of Included Studies Table 2: Results of Included Studies by Level of  
34 870 Intervention  
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36 871 Table 3: Results of Included Studies by PMTCT outcome  
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38 872 Figure 1: PRISMA diagram of search results and screening  
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40 873 Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to  
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42 874 usual (non-integrated care) effect on ART use during pregnancy  
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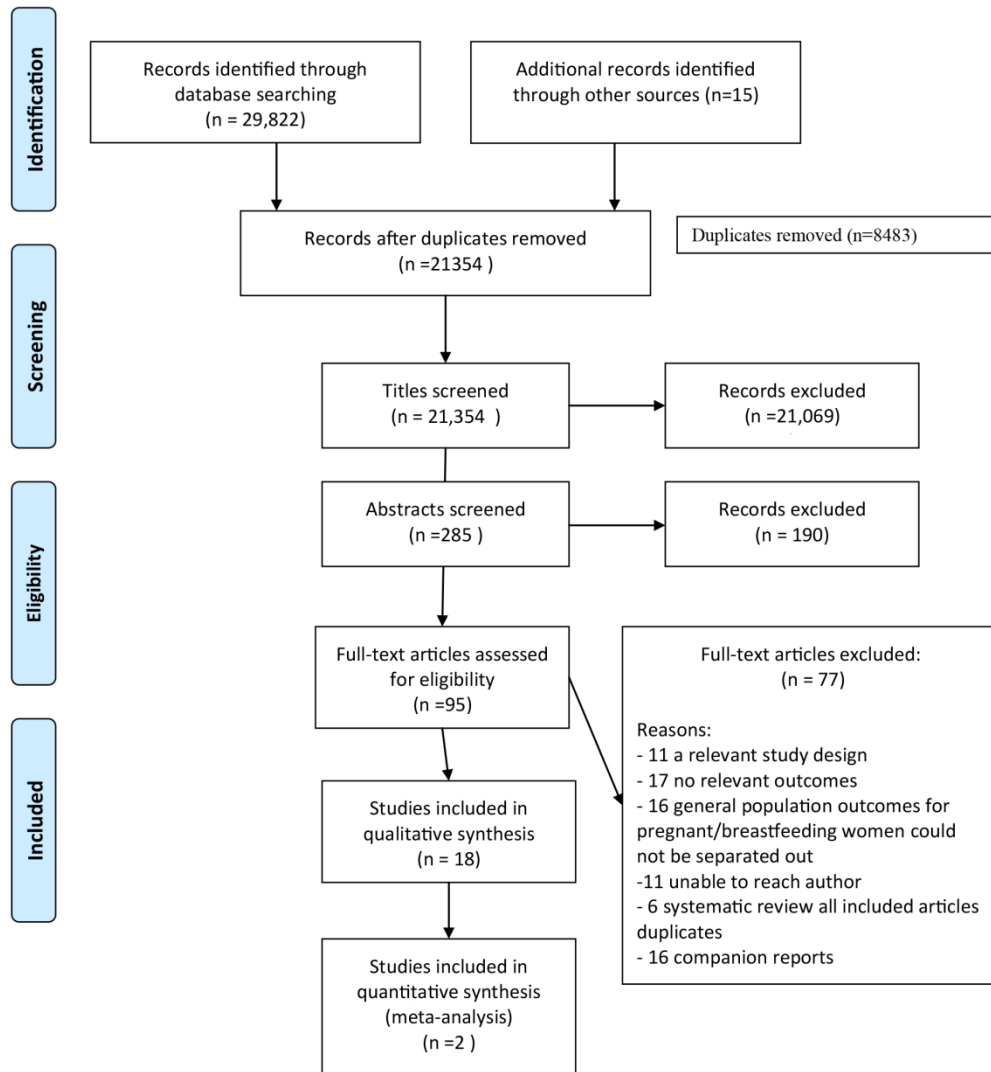


Figure 1: PRISMA diagram of search results and screening

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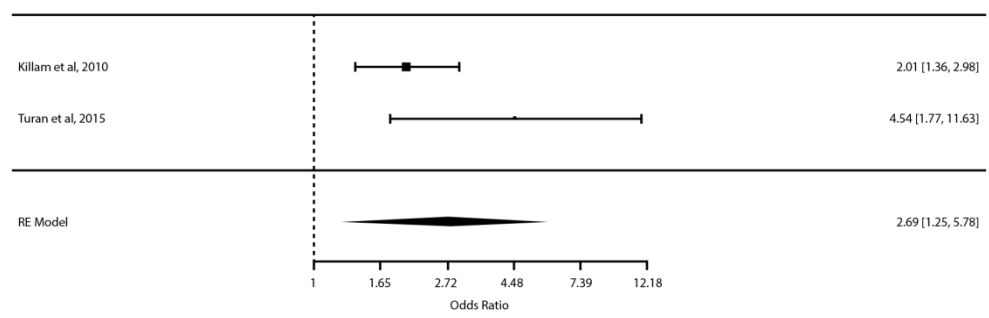
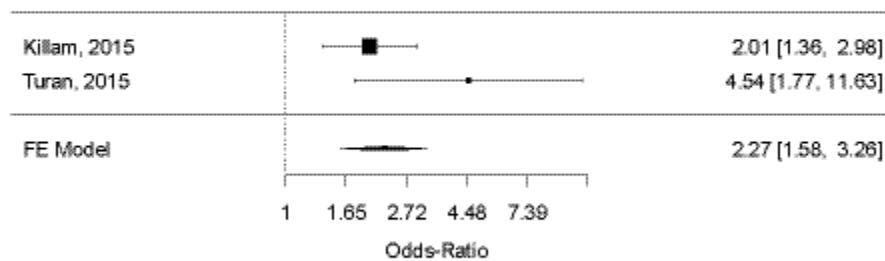


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)



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3 Search Strategy Ovid MEDLINE(R) <1946 to June Week 2 2018>  
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8 Pregnant / Breastfeeding Women

- 9 1 Pregnant Women/ (5226)  
10 2 exp Breast Feeding/ (26666)  
11 3 Milk, Human/ (15697)  
12 4 Infectious Disease Transmission, Vertical/ (12256)  
13 5 fetus/ (68631)  
14 6 exp pregnancy/ (723003)  
15 7 peripartum period/ (427)  
16 8 exp Postpartum Period/ (49233)  
17 9 exp pregnancy complications/ (345863)  
18 10 exp Maternal Health Services/ (35913)  
19 11 pregnan\*.mp,kw,kf. (778553)  
20 12 gestat\*.tw,kw,kf. (144054)  
21 13 breastfeed\*.mp,kw,kf. (13469)  
22 14 (breast adj2 feed\*).mp,kw,kf. (30938)  
23 15 (breast adj2 milk).mp,kw,kf. (8972)  
24 16 breastmilk.tw,kw,kf. (683)  
25 17 human milk.tw,kw,kf. (7840)  
26 18 lactat\*.mp,kw,kf. (165010)  
27 19 (milk adj2 eject\*).tw,kw,kf. (704)  
28 20 (milk adj2 let\*-down).tw,kw,kf. (68)  
29 21 ((expectant or expecting) adj2 wom#n).mp,kw,kf. (182)  
30 22 parturit\*.tw,kw,kf. (11506)  
31 23 birth\*.mp,kw,kf. (259925)  
32 24 childbirth\*.mp,kw,kf. (14074)  
33 25 child-birth\*.mp,kw,kf. (491)  
34 26 deliver\*.mp,kw,kf. (474171)  
35 27 puerper\*.mp,kw,kf. (21074)  
36 28 breastfed.tw,kw,kf. (3524)  
37 29 mtct.tw,kw,kf. (559)  
38 30 pmtct.tw,kw,kf. (725)  
39 31 (vertical adj2 transmission\*).tw,kw,kf. (4511)  
40 32 f?etus\*.mp,kw,kf. (137278)  
41 33 f?etal.mp,kw,kf. (302029)  
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3 34 (breast adj2 fed\*).tw,kw,kf. (5276)  
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5 35 in-utero.tw,kw,kf. (20490)  
6  
7 36 (intrauterine or intra-uterine).tw,kw,kf. (42420)  
8  
9 37 (trans-placent\* or transplacent\*).tw,kw,kf. (5212)  
10  
11 38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)  
12  
13 39 (parent\* adj2 (child\* or infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (28605)  
14  
15 40 mother\*.tw,kw,kf. (147803)  
16  
17 41 (nursing adj2 (infant\* or baby or babies or neonat\* or newborn\*)).tw,kw,kf. (1319)  
18  
19 42 (prenatal\* or pre-natal\*).tw,kw,kf. (70920)  
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21 43 (perinatal\* or peri-natal\*).tw,kw,kf. (51747)  
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23 44 (post-natal\* or postnatal\*).tw,kw,kf. (85370)  
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25 45 (antenatal\* or antenatal\*).tw,kw,kf. (23135)  
26  
27 46 (antepartum\* or ante-partum\*).tw,kw,kf. (4566)  
28  
29 47 (postpartum\* or post-partum\*).tw,kw,kf. (40829)  
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31 48 maternal\*.tw,kw,kf. (172644)  
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33 49 or/1-48 (1763167)

#### HIV/AIDS

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- exp HIV Infections/ (233689)  
exp HIV/ (83825)  
HIV Long-Term Survivors/ (607)  
AIDS Serodiagnosis/ (6107)  
hiv.mp,kw,kf. (263320)  
Human T-Cell Leukemia Virus.mp,kw,kf. (2850)  
htlv-iii.mp,kw,kf. (1652)  
(acquired adj2 immun\* adj2 (syndrome\* or virus\*)).mp,kw,kf. (86030)  
(human\* adj2 immun\* adj2 deficien\* adj2 virus\*).mp,kw,kf. (491)  
(human\* adj2 immun\* adj2 virus\*).mp,kw,kf. (76929)  
(syndrome\* adj2 lymphadenopath\*).tw,kw,kf. (335)  
slim disease.tw,kw,kf. (25)  
lymphadenopathy-associated virus\*.mp,kw,kf. (295)  
lav-htlv-iii.mp,kw,kf. (211)  
sbl-6669.mp,kw,kf. (16)  
lav-2.mp,kw,kf. (25)  
(acquired adj2 immun\* adj2 deficien\* adj2 syndrome\*).tw,kw,kf. (5057)  
(aids adj10 (disease\* or syndrome\*)).mp,kw,kf. (27876)

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3 68 (aids adj1 related).tw,kw,kf. (6614)  
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5 69 htlv\*.tw,kw,kf. (11427)  
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7 70 hiv###mp,kw,kf. (1760)  
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9 71 or/50-70 (325026)  
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11 Patient uptake / dropouts / participation  
12 72 Patient Dropouts/ (6786)  
13 73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)  
14 74 exp Consumer Participation/ (32566)  
15 75 dropout\*.tw,kw,kf. (6483)  
16 76 (uptake or up-take).tw,kw,kf. (248330)  
17 77 (drop\* adj1 out\$1).tw,kw,kf. (8228)  
18 78 (refusal\* or refuse\$1 or refusing).tw,kw,kf. (23366)  
19 79 (patient\* adj2 (elope or elope\$1 or eloping)).tw,kw,kf. (4)  
20 80 (non complian\* or noncomplian\*).tw,kw,kf. (9990)  
21 81 complian\*.tw,kw,kf. (84306)  
22 82 (uncooperat\* or unco-operat\* or un-co-operat\*).tw,kw,kf. (1028)  
23 83 (cooperat\* or co-operat\*).tw,kw,kf. (102475)  
24 84 (non-accept\* or nonaccept\*).tw,kw,kf. (592)  
25 85 accept\*.tw,kw,kf. (279089)  
26 86 (nonparticipat\* or non-participat\*).tw,kw,kf. (1298)  
27 87 participat\*.tw,kw,kf. (322007)  
28 88 (nonadher\* or non-adher\*).tw,kw,kf. (10638)  
29 89 adher\*.tw,kw,kf. (114637)  
30 90 (retain\* or retention\*).tw,kw,kf. (244370)  
31 91 (non-attend\* or nonattend\*).tw,kw,kf. (1453)  
32 92 attend\*.tw,kw,kf. (110407)  
33 93 (comply\* or complies or complian\*).tw,kw,kf. (91550)  
34 94 (non-comply\* or noncomply\* or non-complian\* or noncomplian\*).tw,kw,kf. (10004)  
35 95 reluctan\*.tw,kw,kf. (8504)  
36 96 ((healthcare or care or advice or medical or information) adj3 seek\$3).tw,kw,kf. (15252)  
37 97 (disengag\* or dis-engag\*).tw,kw,kf. (2812)  
38 98 engag\*.tw,kw,kf. (82419)  
39 99 avoid\*.tw,kw,kf. (237366)  
40 100 ut.fs. (144195)  
41 101 ignor\*.tw,kw,kf. (27215)  
42 102 reject\*.tw,kw,kf. (82472)  
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3 103 (non-embrac\* or nonembrac\*).tw,kw,kf. (0)  
4 104 (un-embrac\* or unembrac\*).tw,kw,kf. (1)  
5 105 (embrace\* or embracing).tw,kw,kf. (7691)  
6 106 (un-accept\* or unaccept\*).tw,kw,kf. (14546)  
7 107 (unadher\* or un-adher\*).tw,kw,kf. (14)  
8 108 no-show\*.tw,kw,kf. (484)  
9 109 (follow\* adj1 up).tw,kw,kf. (638770)  
10 110 incent\*.tw,kw,kf. (17823)  
11 111 enabl\*.tw,kw,kf. (214935)  
12 112 disincent\*.tw,kw,kf. (859)  
13 113 utiliz\*.tw,kw,kf. (319558)  
14 114 (inclin\* or disinclin\*).tw,kw,kf. (12034)  
15 115 or/72-114 (2984236)  
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24 Study type / characteristics  
25 116 randomized controlled trial.pt. (387105)  
26 117 exp Randomized controlled trial/ (387132)  
27 118 exp Randomized Controlled Trials as Topic/ (97414)  
28 119 clinical trial.pt. (490674)  
29 120 Double-Blind Method/ (128228)  
30 121 Placebos/ (32662)  
31 122 clinical trials as topic/ (171490)  
32 123 evaluation research/ (119973)  
33 124 program evaluation/ (47548)  
34 125 Feasibility Studies/ (45412)  
35 126 Pilot Projects/ (85700)  
36 127 Evaluation Studies as Topic/ (119973)  
37 128 Cost-Benefit Analysis/ (61646)  
38 129 (random\* or non-random\* or unrandom\* or nonrandom\*).mp,kw,kf. (874470)  
39 130 placebo\*.mp,kw,kf. (168179)  
40 131 rct\*1.tw,kw,kf. (17367)  
41 132 ((singl\* or doubl\* or trebl\* or tripl\*) adj1 (mask\* or blind\* or dumm\*)).mp,kw,kf. (176744)  
42 133 evaluat\*.mp,kw,kf. (2416275)  
43 134 effectiv\*.mp,kw,kf. (1149619)  
44 135 sustainab\*.mp,kw,kf. (23041)  
45 136 feasib\*.mp,kw,kf. (177882)  
46 137 appropriateness.mp,kw,kf. (12458)  
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4 139 impact\*.mp,kw,kf. (537916)  
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6 140 (pilot adj2 (project\* or study or studies)).mp,kw,kf. (103303)  
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8 141 cost-effectiv\*.mp,kw,kf. (73309)  
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10 142 (cost\*1 adj2 benefit\*1).mp,kw,kf. (69472)  
11 143 (interrupt\* adj2 time).mp,kw,kf. (1224)  
12 144 or/116-143 (4705604)  
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14 Lower middle income countries

- 15 145 Developing Countries/ (63034)  
16  
17 146 (Imic or Imics or lami countr\*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)  
18  
19 147 ((developing or less\* developed or under developed or underdeveloped or middle income  
20 or low\* income or underserved or under served or deprived or poor\*) adj (countr\* or nation? or  
21 population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)  
22  
23 148 (Afghan\* or Albania\* or Algeria\* or Angola\* or Antigua\* or Barbud\* or Argentin\* or  
24 Armenia\* or Aruba\* or Azerbaijan\* or Bahrain\* or Bangladesh\* or Barbad\* or Benin\* or Byelarus\*  
25 or Byelorus\* or Belarus\* or Belorus\* or Beliz\* or Bhutan\* or Bolivia\* or Bosnia\* or Herzegovin\* or  
26 Hercegovin\* or Botswan\* or Brasil\* or Brazil\* or Bulgaria\* or Burkina Faso\* or Burkina Fasso\* or  
27 Upper Volta\* or Burundi\* or Urundi\* or Cambodia\* or Khmer Republic or Kampuchea\* or  
28 Cameroon\* or Cameron\* or Cape Verde\* or Central African Republic or Chad\* or Chile\* or China  
29 or chinese or Colombia\* or Comoros\* or Comoro Islands or Comores or Mayott\* or Congo\* or  
30 Zair\* or Costa Rica\* or Cote d'Ivoire or Ivory Coast or Croatia\* or Cuba\* or Cyprus or cyprian or  
31 Czechoslovakia\* or Czech Republic or Slovakia\* or Slovak Republic or Djibouti\* or French  
32 Somaliland or Dominica\* or East Timor or East Timur or Timor Leste or Ecuador\* or Egypt\* or  
33 United Arab Republic or El Salvador\* or Eritrea\* or Estonia\* or Ethiopia\* or Fiji\* or Gabon\* or  
34 Gambia\* or Gaza\* or Georgia Republic or Georgian Republic or georgian or Ghana\* or Gold  
35 Coast or Greece or greek or Grenada\* or Guatemala\* or Guinea\* or Guam\* or Guiana\* or  
36 Guyana\* or Haiti\* or Hondura\* or Hungar\* or India\* or Maldiv\* or Indonesia\* or Iran\* or Iraq\* or  
37 Isle of Man or Jamaica\* or Jordan\* or Kazakh\* or Kenya\* or Kiribati\* or Korea\* or Kosovo\* or  
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42 Mongolia\* or Montenegr\* or Morocc\* or Ifni\* or Mozambiq\* or Myanmar\* or Myanma or Burma\* or  
43 Namibia\* or Nepal\* or Netherlands Antill\* or New Caledonia\* or Nicaragua\* or Niger\* or Northern  
44 Mariana Island\* or Oman\* or Muscat\* or Pakistan\* or Palau\* or Palestin\* or Panama\* or Paragua\*  
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5 Tome\* or Saudi Arabia\* or saudi or Senegal\* or Serbia\* or Montenegr\* or Seychelles or Sierra  
6 Leone or Slovenia\* or Sri Lanka\* or Ceylon\* or Solomon Islands or Somalia\* or South Africa\* or  
7 Sudan\* or Surinam\* or Swaziland or swazi or Syria\* or Tajik\* or Tadjik\* or Tadhik\* or Tanzania\*  
8 or Thailand or thai or Togo or Togolese Republic or Tonga\* or Trinidad\* or Tobag\* or Tunisia\* or  
9 Turkey or turkish or Turkmenistan\* or Turkmen\* or Uganda\* or Ukrain\* or Urugua\* or USSR or  
10 Soviet Union or Union of Soviet Socialist Republics or Uzbek\* or Vanuat\* or New Hebrides or  
11 Venezuela\* or Vietnam\* or Viet Nam\* or West Bank or Yemen\* or Yugoslavia\* or Zambia\* or  
12 Zimbabw\* or Rhodesia\* or cabo verd\*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)  
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21 Full topic

22 150 49 and 71 and 115 and 144 and 149 (3309)

23 151 exp animals/ not (exp animals/ and exp humans/) (4003250)

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26 Full topic minus animal-only studies

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## Risk of Bias within included studies

| Study                 | Random Sequence Generation | Allocation Concealment | Blinding of Participants and Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Outcome Reporting |
|-----------------------|----------------------------|------------------------|--|--------------------------------|-------------------------|-----------------------------|
| Aliyu; 2016           | Low                        | Unclear                | High                                   | High                           | Low                     | Low                         |
| Dryden-Peterson; 2015 | Unclear                    | Low                    | High                                   | High                           | High                    | Low                         |
| Ezeanolue; 2015       | Low                        | Low                    | High                                   | Unclear                        | High                    | Low                         |
| Geelhoed; 2013        | Unclear                    | Unclear                | Unclear                                | Unclear                        | High                    | High                        |
| Kieffer; 2011         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Killam; 2010          | Unclear                    | High                   | High                                   | Unclear                        | High                    | Unclear                     |
| Mwapasa; 2017         | Low                        | Unclear                | High                                   | Unclear                        | High                    | Low                         |
| Odeny; 2014           | Low                        | Low                    | High                                   | Unclear                        | Low                     | Unclear                     |
| Oyedun; 2017          | Low                        | Unclear                | High                                   | Unclear                        | High                    | Unclear                     |
| Phiri; 2017           | Unclear                    | High                   | High                                   | Low                            | Low                     | Low                         |
| Reynolds; 2010        | Unclear                    | Unclear                | High                                   | High                           | High                    | Unclear                     |
| Richter; 2014         | Unclear                    | High                   | High                                   | High                           | High                    | Low                         |
| Rotheram-Borus; 2014  | Unclear                    | Unclear                | High                                   | High                           | Unclear                 | Low                         |
| Rustagi; 2016         | Low                        | Unclear                | Unclear                                | Unclear                        | Unclear                 | Low                         |
| Tomlinson; 2014       | Low                        | Unclear                | High                                   | Low                            | Low                     | Low                         |
| Turan; 2015           | Low                        | High                   | High                                   | High                           | High                    | Low                         |
| Weiss; 2014           | Unclear                    | Unclear                | Unclear                                | Unclear                        | Unclear                 | High                        |
| Yotebieng; 2016       | Low                        | Unclear                | High                                   | High                           | High                    | High                        |



# PRISMA 2009 Checklist

| Section/topic                      | #  | Checklist item  | Reported on page # |
|------------------------------------|----|---|--------------------|
| <b>TITLE</b>                       |    |   |                    |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.   | 1                  |
| <b>ABSTRACT</b>                    |    |   |                    |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3-4                |
| <b>INTRODUCTION</b>                |    |   |                    |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.  | 5-6                |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 6                  |
| <b>METHODS</b>                     |    |   |                    |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.   | 7                  |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | 7                  |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 8                  |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.   | 8                  |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).   | 8-9                |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | 8-9                |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.   | 9                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | 10                 |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).   | 10                 |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.   | 10                 |



# PRISMA 2009 Checklist

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| Section/topic                 | #  | Checklist item   | Reported on page # |
|-------------------------------|----|--|--------------------|
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).   | 10                 |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.   | N/A                |
| <b>RESULTS</b>                |    |  |                    |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Figure 1           |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.   | 11-12<br>Table 1   |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | 12-13<br>Table 2   |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 14-20<br>Table 3   |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 13<br>Figure 2     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 10                 |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | N/A                |
| <b>DISCUSSION</b>             |    |  |                    |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | 20-23              |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | 4, 23              |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 24                 |
| <b>FUNDING</b>                |    |  |                    |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.   | 25                 |





# PRISMA 2009 Checklist

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