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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.

Conclusions:

The evidence on effectiveness of interventions to improve uptake and retention of mothers and infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal care may improve ART use during pregnancy. Future studies to replicate promising approaches are needed. Improved reporting of key methodological criteria will facilitate interpretation of findings and improve the utility of evidence to PMTCT program planners.

Systematic review registration: PROSPERO-CRD42015020829

Key Words: HIV, prevention of mother to child transmission, interventions, retention, uptake

Strengths and Limitations of this review:

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

Introduction:

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

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

of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of included studies reported PMTCT outcomes, this was not a primary focus of the review. A second review focused on postpartum retention of women in PMTCT and ART care (14). This review focused on a limited portion of the PMTCT cascade. A third review (15) focused on interventions to improve PMTCT service delivery and promote retention. This review included a range of study designs and studies conducted in both high and low-middle income countries and as such, is of less value as a guide to decision making for PMTCT policy and programming in LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by: lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high income country studies where the context of PMTCT care is often substantially different than in LMICs.

This review was developed in collaboration with knowledge users from the Malawi Ministry of Health's HIV treatment and care technical working group. The objective of this current review was to identify what interventions at the patient, provider, or health system level are effective compared to no intervention or usual care in improving uptake and retention of HIV infected mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health services in LMICs, this review is targeted to provide guidance for PMTCT policy and programming in LMICs, and therefore included a broad range of intervention categories, as well as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.

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). 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).

Eligibility Criteria:

We included studies reporting the effectiveness of interventions in improving uptake and/or retention of HIV-infected 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 results could be abstracted. No restriction was placed based on language of publication, publication status, study time frame, or duration of follow-up.

Information Sources and Literature Search:

A search strategy was developed in consultation with an experienced information specialist (MA) and peer reviewed by two additional information specialists (EC, BS) using the Peer Review of Electronic Search Strategies checklist (22). The following databases were searched from inception to July 31, 2015 and subsequently updated using the same search strategy for the period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV, pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science, Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE, ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library, WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov. Several databases planned for inclusion in our search were no longer available or not accessible by our group at the time of the search and were therefore not included: AIDS Education Global Information System, British Library Catalogue, and the New York Academy of Grey Literature. In addition, we searched reference lists of included articles, and contacted several experts in the field to inquire about eligible unpublished or in progress studies. See additional file for complete MEDLINE search strategy.

Study Selection and Data Collection Process:

A screening checklist was developed and piloted by two authors (LPR, MvL) independently on a sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement. Two authors (LPR, MvL) then independently screened citations in two phases; first the titles,

then abstracts were screened, and second, the full-text articles were screened. Translation software was utilized to screen articles at the titles and abstracts level, with no non-English articles remaining at the full article review phase. A data abstraction form was created using the EPOC data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in screening and data extraction. A calibration exercise was conducted with completed data extraction forms compared and discussed for each of the first three articles to ensure consistency; data extraction was then completed for the remaining articles independently and in duplicate by two authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each study included: population, intervention, comparator, context, outcomes, study design, time frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes were percentage of HIV-infected women receiving or initiated on ART prophylaxis or treatment, percentage of infants born to HIV infected mothers receiving or initiated on ART prophylaxis, and percentage of women and infants retained in PMTCT care/completing the ART regimen as defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants completing post-exposure HIV testing 6 weeks following termination of breast feeding for all infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV; adverse events; major or minor congenital malformations; small for gestational age; pre-mature delivery; still birth; and infant death within first two years of life (18).

When necessary to clarify published data or to obtain unpublished data, we contacted primary authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions,

and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to calculate risk ratios were not available in the publication. Three responded and provided the requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional data as they were submitting the manuscript for publication.

Methodological Quality/Risk of Bias Appraisal:

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

Data Synthesis:

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

Results:

Literature Search:

A total of 29,837 articles were identified through the database and hand search and provided by authors. 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).

Study Characteristics:

Study characteristics are outlined in Table 1.

Table 1: Characteristics of Included Studies

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
Ezeanolue; 2015	Patient	Mixed Methods Including Small Cluster RCT	Nigeria (Enugu state)	Churches with >20 baptisms/yr for past 3 yrs, 1 church/per community with churches at least 5 k apart . Self-identified pregnant ≥18 years who attended any church site;	Monthly baby showers offered women educational game shows (to test their knowledge of healthy pregnancies including PMTCT) and contact point for follow-up, Mama Packs (for essential items during pregnancy) and essential lab tests (including HIV)	Usual care	• Outreach services	Clusters (40 churches) 3002 patients enrolled of these, I (n = 41) and C (n = 32) tested positive for HIV	• % HIV positive: 2% overall • Maternal age (mean): (I = 29.3, C = 29.7) • Marital status: (I = 0% divorced, 93% married, 0.5% separated, 7% single; C = 0.15% divorced, 94% married, 0.5% separated, 5.02% single) • Education level: (I = 27% primary/none, 58% secondary, 14% tertiary; C = 24% primary/none, 55% secondary, 20% tertiary) • Age at first pregnancy: (I = 63% <24.9, 30% 25-34.9, 1% > 35; C = 60% <24.9, 35% 25-34.9, 2% > 35) • Employment status: (I = 35% full-time employed, 24% part-time employed, 38% unemployed; C = 37% full-time	1) ART during pregnancy 2) Retention in care at 6-8 week postpartum

									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 neverapine infant dose. Pregnant women instructed on how to store and administer the neverapine 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 neverapine dose administration.	Usual care	• Self-management • Educational outreach	Clusters: (n = 10) Patients: I (n = 116 total), C (n = 87 total)	• Maternal age (mean): (I = 27.4, C = 28.4) • 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) • Education level: (I = 16% none, 58% primary, 19% secondary, 7% post-secondary; C = 19% none, 51% primary, 25% secondary, 5% post-secondary) • 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)	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 ANCs.	Time-matched health education sessions	• Group (couple) vs individual care	Clusters: (n = 12 antenatal clinics); Patients: (n = 239 couples)	• % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive • Maternal age (mean): (I = 28.3; C = 28.1) • Education level: (I = 57% < grade 12, 43% grade 12 or more; C = 50% < grade 12, 51% grade 12 or more) • Employment status: (I = 27% employed, 74% unemployed; C = 30% employed, 70% unemployed)	1) ART detected in mother blood samples at birth 2) ART detected in infants blood at birth 3) Infant HIV infection rate at 6 weeks
Yotebieng; 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

			(Kinshasa)	women, <=32 weeks gesationt, 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) • Marital status: (I = 82.8% married/cohabiting, 17.2% divorced/separated/widow/never married; C = 82.9% married, 17.1% divorced/separated/widow/never married) • Education level (median): I = 10.0 (8.0–12.0); C= 10.0 (8.0–12.0)	postpartum 2) Uptake of PMTCT services through to 6 weeks postpartum 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 • 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)) • Married/lives with partner (I = 118.8%, C = 23.3%) • Education level: (I = 15% primary/none, 79.3% secondary, 5.7% tertiary; C = 16.5% primary/none, 80% secondary, 3.5% tertiary) • Employed (I = 51.3%, C = 39.3%)	1) ART from the 28th week of pregnancy (AZT or HAART) 2) ART during labor (AZT or HAART 3) NVP or HAART during labor 4) Infant NVP at birth 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

					provision of PMTCT and to enhance confidence and counseling skills.					
Dryden-Peterson; 2015	Provider/System	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 communication technology • 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%)	• Maternal age (median/quartiles): (I = 28 (25,33); C = 29(26,33)) • Marital status: (I = 9% married, 89% single/divorced/widowed, 2% unknown; C = 10% married, 89% single/divorced/widowed, 2% unknown) • Education level: (I = 6% primary/none, 83% secondary, 8% university, 3% unknown; C = 9% primary/none, 73% secondary, 16% university, 1% unknown)	ART initiation by 30 wks gestation
Mwapasa; 2017	Provider/System	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 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 • The use of information and communication technology	Clusters: (n = 30 health centers) Patients: (n = 1350 women)	• 1350 women (MIP = 34.1%; MIP+SMS = 36.5%; SOC = 29.3%) • 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) • 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) • 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%	1) Maternal retention in care at 12 months postpartum trial data 2) Infant retention in care at 12 months postpartum trial data 3) Maternal retention in care at 12 months using MOH definitio 4) Infant retention in care at 12 months using MOH definition

									missing; SOC = 40.9% none, 50.0% primary, 9.1% secondary and above, 0% missing)	
Oyeleun; 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. 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)	• 511 women (I = 51.7%; C = 48.3%) • Maternal age (median): I = 27 (23-30); C = 27 (23-30) • Marital status: (I = 94.7% married, 5.3% others; C = 93.5% married, 6.5% others) • 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)	1) ART initiated within 2 week of enrolment 2) Retention in care at 6 months 3) Infants starting prophylaxis within 72 hours 4) infant HIV testing at 6-10 weeks
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. 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. 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 • 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)	• 1269 women (FBPS = 33.7%, CBPS = 31.0%, SOC = 35.2%) • Maternal age (median across all 3 arms): 27 (IQR 22–31) included age 15-21 as youngest group • 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	1) ART uptake 2) Retained in care at 1 year: 3) Retained in care at 2 years trial data 4) Retained in care at 2 years MOH definition 5) Infant HIV tested at 6 weeks 6) Infant HIV infected at 6 weeks

					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.					
Tomlinson: 2014	Provider /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	• Role expansion or task shifting • Outreach services	Clusters: (n = 30) Patients: (n = 3957)	Maternal age (median): (I = 23; C = 23) - 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) - 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)	1) Infant HIV testing by 6 weeks 2) Infant HIV infection at 12 weeks
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	• Role expansion/task shifting Integration • Packages of care	Clusters: (n= 12 hospitals) Patients: (n = 369)	• 369 HIV positive patients eligible and assessed for ART initiation (I = 46.6%; C = 53.4%) • Maternal age (years): I = 26	1) Maternal ART initiation 2) Maternal-infant retention in care at 6 week postpartum 3) Maternal-infant

				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) • 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) • 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) • 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 • Educational meetings	Clusters: (n = 6)	Not available	1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 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) Patients: (n = 31536)	• % HIV positive: (I = 21.8%; C = 22.2%) • Maternal age (mean): (I = 27.5; C = 27.3) • Marital status: (I = 88.1% married, 5.4% not married, 6.5% unknown; C= 89.1% married, 6.7% not married, 4.2% unknown) • Education level: (I =3.3% none, 79.8%	ART initiation during pregnancy

									primary, 1.2% secondary, 15.7% tertiary; C = 3.2% none, 80.0% primary, 2.7% secondary, 14.1% tertiary)	
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)	• % HIV positive: 29.3% (388/1324) • 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+) • Married/with regular live-in partner: (I = 86.7%; C = 88.6%) • 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) • % first pregnancy: (I = 13.8%; C = 15.0%) • Employment status: (I = 17.9% employed; C = 20.2% employed)	1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks
Rother am-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 • Outreach services	Clusters: (n = 26 [2 later removed due to low #s of pregnant women]); Patients: (n = 1144 eligible pregnant women)	• Women living with HIV: (I = 149 (25.5%); C =146 (26.7%) • Mean maternal age (SD) (I = 26.5 (5.5); C = 26.3(5.6) • Married/lives with partner: (I =377 (58.5%); C =324 (54.6%)) • Mean (SD) highest education level: (I = 10.3, Primapara I = 222 (34.5%); C = 200 (33.7%)) • Employment status: (I = 20% ever employed; C = 17.5% ever employed)	1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART at onset of labor 4) Infant prophyaxis within 24 hours of birth 5) AZT dispensed for infant and medicated as prescribed 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	• Years of PMTCT initiation: (I = 17% before 2005, 50% 2005-2008, 22% after 2008; C = 17% before 2005, 67% 2005-2008, 17% after 2008)	1) ART in pregnancy 2) Infants HIV tested by 6-8 weeks

				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				• Monthly ANC visits Quintiles: I = 12% <65, 18% 65 to <86.9, 24% 86.9 to<122.2, 29% 122.2 to <185.3, 18% 185.3+; C =28% <65, 22% 65 to <86.9, 17% 86.9 to<122.2, 11% 122.2 to <185.3, 22% 185.3+	
Turan; 2015	System	Cluster RCT	Kenya (Nyanza Province)	Pregnant HIV positive women >= 18, not enrolled in HIV care at baseline and their infants; Health facilities providing ANC, PMTCT, and HIV services with ≥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	• Integration	Clusters: (n = 12) Patients: (n = 1172 HIV infected pregnant women)	• HIV positive: 1172 HIV positive pregnant women enrolled (I = 48.5%, C = 51.5%) • Maternal age, mean (SE): I = 25.0 (0.19), C = 24.8 (0.18) • Marital status: (I = 84% married, 8% single/separated /divorced, 8% widowed; C = 84% married, 8% single/separated /divorced, 8% widowed) • Education level: (I = 85% none/primary, 15% secondary or more; C = 89% none/primary, 11% secondary or more)	1) ART during pregnancy 2) ART during Labor 3) ART after birth 4) Infant ART after birth 5) ART use throughout 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 infected at 6 weeks 10) Infants HIV tested by end of study (up to 12 months) 11) Infants infected at 9 months

The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge design, and 2 RCTs. The number of clusters ranged from six to 40, and participants across all study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan Africa between 2005 and 2016. Half of included studies reported multifaceted interventions including 2 or more EPOC category components (9/18) and as a result several were categorized at more than one intervention level: patient (4), provider (1), system (7), patient/provider (1), or

provider/system (5). Interventions directed all or in part to the health system level were most common (12/18). Integration (5/18), role expansion or task shifting (5/18), outreach services (4/18), and use of information and communication technology (4/18) were the most common EPOC intervention categories employed alone or as part of a complex intervention. All included studies were conducted in Sub-Saharan Africa.

Reporting of population characteristics varied widely across studies as did outcome definitions. Seven studies limited participation to pregnant women 17-18 years of age or older; median ages across the studies ranged from 23 to 29.7 years. Marital status was reported in fourteen studies, and varied widely from 9% to 99% of women who were married or had a live-in partner. Maternal education level was reported in twelve studies; 5 studies reported the majority of women having no or primary education, 5 studies reported the majority of women having received secondary education, and, two reported mean/median years of education (10.3 years, 10 years (range 8-12years)). Maternal employment (6/18) and parity (2/18) status were reported in a minority of studies (Table 1). No pre-specified adverse events were reported in the identified studies.

Reported outcomes varied substantially across studies, with few studies within intervention categories reporting comparable outcomes. For example, 5 studies reported interventions employing integration alone (2) or in combination with other interventions (3), with only 1 PMTCT outcome in common among the two studies employing integration alone. The most commonly reported outcomes were maternal ART use during pregnancy and labor and delivery, infant prophylaxis at birth, and infant HIV testing and infant HIV positive rates at 6-8 weeks.

Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance.

As a result of the multifaceted nature of the majority of interventions employed, and variability in PMTCT outcomes reported, the ability to combine results statistically was limited.

Methodological Quality:

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

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; 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

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

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

Descriptive Synthesis:

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

Table 3: 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 services	Monthly baby showers	Usual care	1) ART during pregnancy: 24/41 (65%) 2) Retention in care at 6-8 week	1) ART during pregnancy: 12/32 (50%) 2) Retention in care at 6-8 week	1) 1.56 (0.93 - 2.62) 2) 0.92 (0.75-1.12)	1) AOR 2.8 (1.02-4.79) 2) AOR 0.39 (0.04-3.99)

					postpartum: 33/41(81%)	postpartum: 28/32(88%)		
Reynolds; 2010	Patient	• Self-management • 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%) 2) ART detected in infants blood at birth: 12/13 (92%) 3) Infant HIV positive:: 1/30 (3.3%)	1) ART detected in mother blood samples at birth: I6/12 (50%) 2) ART detected in infants blood at birth: 9/12 (75%) 3) Infant HIV positive: 3/39 (7.7%)	1) 1.50 (0.78-2.88) 2) 1.23 (0.86-1.77) 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%) 2) Uptake of PMTCT services through to 6 wks postpartum:146/216 (67.6%) 3) HIV positive infants at 6 weeks: 5/169 (3.0%)	1) Retention in care at 6 weeks postpartum: 157/217 (72.4%) 2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%) 3) HIV positive infants at 6 weeks: 6/156 (3.9%)	1) 1.11(1.00-1.23) 2) 1.26(1.08-1.48) 3) 0.77(0.24-2.47)	1) ARD 1.13 (1.02-1.26) 2) ARD 1.31 (1.12-1.54) 3) –
Richter, 2014	Patient/Provider	• Role expansion or task shifting • Educational meetings	Peer Mentor led educational meetings	Usual Care	1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%) 2) ART during labor (AZT or HAART): 282/377 (74.8%); 3) NVP or HAART during labor: 361/377 (95.8%) 4) Infant NVP at birth: 364/377 (96.6%) 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%) 2) ART during labor (AZT or HAART): 334/466 (71.7%) 3) NVP or HAART during labor: 456/466 (97.9%) 4) Infant NVP at birth: 451/466 (96.8%) 5) AZT dispensed for infant and medicated as prescribed: 374/466	1) 0.92 (0.89-0.96) 2) 1.04 (0.96-1.13) 3) 0.98 (0.95-1.00) 4) 1.00 (0.97-1.02) 5) 1.15 (1.09-1.21)	1) AOR 0.44 (0.26,0.74) 2) AOR 1.16(0.44, 3.02) 3) AOR 0.53 (0.20, 1.41) 4) AOR 1.00 (0.36, 2.79) 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-Peterson; 2015	Provider/System	• The use of information and communication technology • Education	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/System	• Integration • The use of information and communication technology	MIP= integration of antenatal and HIV care, routine patient tracing 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% MIP+SMS 115/493 2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3% MIP+SMS 82/399, 20.1% 3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4% MIP+SMS 332/493, 67%. 4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4% MIP+SMS 323/399, 80.9%	1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7% 2) Infant retention in care at 12 months postpartum trial data: SOC 32/300,10.7 3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1% 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) 2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82) 3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06) 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) 2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31) 3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05) 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/System	• Continuous quality improvement	QI teams established, coaching, and collaborative meetings	Routine MOH support	1) ART initiated within 2 week of enrolment: 261/264 = 98.9% 2) Retention in care at 6 months. 117/264 = 44.3% 3) Infants starting prophylaxis within 72 hours : 138/209 = 66**%** 4) Infant HIV testing at 6-10 weeksI: 102/209 = 48.8%;	1) ART initiated within 2 week of enrolment: 233/247 = 94.3% 2) Retention in care at 6 months. 102/247 = 41.3% 3) Infants starting prophylaxis within 72 hours 145/194 = 74.7% 4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%	1) 1.05 (1.01-1.08) 2) 1.07 (0.88-1.31) 3) 0.88 (0.78-1.00) 4) 1.93 (1.46-2.55)	1) -- 2) ARR 1.08(0.78, 1.49) 3) ARR 0.95 (0.84, 1.07) 4) ARR 1.76(1.27, 2.42)
Phiri; 2017	Provider/System	• Role expansion or task shifting outreach services • The use of information and communication technology	FBPS – facilty based peer support from mentor mothers CBPS- community based peer support from mentor mothers	SOC- standard of care	1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%) 2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%) 3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394 (54%) 4) Retained in	1) ART uptake: SOC- 361/447(81%) 2) Retained in care at 1 year: SOC- 261/361 (74%) 3) Retained in care at 2 years (trial data): SOC- 169/447 (38%) 4) Retained in care at 2 years	1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06-1.18) 2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10) 3) SOC vs FBPS 1.38(1.19-1.60), SOC vs CBPS 1.42	1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18) 2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20) 3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30) 4) --

					care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%) 5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%) 6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%)	(MOH definition): SOC- 255/447(57%) 5) Infant HIV test at 6 weeks: SOC- 169/273(62%) 6) Infant HIV postive at 6 weeks: SOC- 2/169(1%)	(1.22-1.65) 4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43) 5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38) 6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09)	5) -- 6) ---
Tomlinson: 2014	Provider/System	• Role expansion or task shifting • Outreach services	10 structured home visits from community health workers addressing PMTCT and newborn care	3 home visits from community health workers providing support in accessing social welfare grants	1) Infant HIV testing by 6 weeks: 420/571(73.6%) 2) Infant HIV positive at 12 weeks: 28/568 (4.9%)	1) Infant HIV testing by 6 weeks: 465/698(66.6%) 2) Infant HIV positive at 12 weeks: 32/697 (4.6%)	1) 1.10 (1.03-1.19) 2) 1.07 (0.65-1.76)	1) ARR 1.10 (0.97, 1.25) 2) ARR 1.07 (0.69,1.66)
Aliyu; 2016	System	• Role expansion /task shifting Integration • Packages of care	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%) 3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)	1) Maternal ART initiation for PMTCT: 77/197 (39%), 2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%) 3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%)	1) 2.47 (2.07-2.95) 2) 9.44 (5.60-15.40) 3) 11.40 (6.40-20.34)	1) ARR 3.3 (1.4-7.8) 2) ARR 9.1 (5.2-15.9) 3) ARR 10.3(5.4-19.7)
Geelhoed; 2013	System	• Integration • Educational meetings	Integrated maternal child health and HIV care	Usual Non-integrated care	1) ART in labor: post intervention:112/121 (93%) 2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%); 3) Infants HIVpostive: post intervention: 9/123 (7%)	1) ART in labor: intervention phase =93/96(97%) 2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%) 3) Infants HIV positive: intervention phase: 7/60(12%)	1) 0.96 (0.90-1.02) 2) 0.93 (0.88-0.97) 3) 0.63 (0.25-1.60)	-- -- --
Killam; 2010	System	• Integration	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; 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%) 2) Infant HIV testing by 8 wks: I172/187 (92.0%)	1) Maternal postpartum clinic attendance: 22/187 (11.8%) 2) Infant HIV testing by 8 wks: 154/181 (85.1%)	1) 1.66 (1.03-2.70) 2) 1.08 (1.00-1.16)	-- -
Rotheram-Borus; 2014	System	• Role expansion or task shifting • Outreach services	Antenatal and postnatal home visits from community health workers	Usual care	1) ART prior to labor: 169/179 (94.4%) 2) AZT or HAART during labor: I164/179 (91.6%) 3) NVP or HAART at onset of labor: 166/179 (92.7%) 4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%) 5) Infant ART after birth: 172/179 (96.1%) 6) Infant HIV testing at 6 weeks: 155/160 (96.9%)	1) ART prior to labor: 149/159 (93.7%) 2) AZT or HAART during labor: 147/159 (92.5%) 3) NVP or HAART at onset of labor: 142/159 (89.3%) 4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%) 5) Infant ART after birth: 142/159 (89.3%) 6) Infant HIV testing at 6 weeks: 132/140 (94.3%)	1) 1.01 (0.95-1.06) 2) 0.99 (0.93-1.06) 3) 1.04 (0.97-1.11) 4) 1.08 (1.01-1.15) 5) 1.08 (1.01-1.14) 6) 1.03 (0.98-1.08)	1) AOR 1.08 (0.42, 2.80) 2) AOR 0.87 (0.39, 1.95) 3) AOR 1.52(0.70, 3.31) 4) AOR 2.94(1.41, 6.12) 5) AOR 2.95 (1.12, 7.73) 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%) 2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)	1) ART in pregnancy: 664/1037(64%) 2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)	1) 1.07 (1.00-1.14) 2) 1.23 (1.09-1.40)	-- --
Turan; 2015	System	• Integration	Integrated HIV and antenatal care	Usual, non-integrated care	1) ART during pregnancy: 138/173 (80%) 2) ART during Labor: 28/173 (16%) 3) ART after birth: 22/173 (13%) 4) Infant ART after birth: 50/173 (29%) 5) ART throughout all 3 PMTCT periods: 37/176 (21.0%) 6) Infant HIV testing before 3 months: 143/569 (25%) 7) Infant HIV testing at 9 months: 361/569 (63%) 8) Infants HIV tested by 6 weeks: 143/568 (25%) 9) Infants HIV positive at 6 weeks: I6/143 (4.2%)	1) ART during pregnancy: 75/152 (49%) 2) ART during Labor: 84/152 (55%) 3) ART after birth: 57/152 (38%) 4) Infant ART after birth: 106/152 (70%) 5) ART throughout all 3 PMTCT periods: 23/153 (15.0%) 6) Infant HIV testing before 3 months: 106/603 (18%) 7) Infant HIV testing at 9 months: 326/603 (54%) 8) Infants HIV tested by 6 weeks: 106/594 (18%) 9) Infants HIV positive at 6 weeks: 7/106 (6.6%)	1) 1.61 (1.35-1.93) 2) 0.29 (0.20-0.42) 3) 0.34 (0.22-0.53) 4) 0.41 (0.32-0.54) 5) 1.40 (0.87-2.24) 6) 1.43 (1.14-1.79) 7) 1.17 (1.07-1.29) 8) 1.41 (1.13-1.76) 9) 0.64 (0.22-1.84) 10) 1.18 (1.08-	1) AOR 4.05 (2.0, 8.0) 2) AOR 0.16 (0.04, 0.68) 3) AOR 0.24 (0.08, 0.70) 4) AOR 0.18 (0.09, 0.35) 5) AOR 1.72 (0.85, 3.48) 6) AOR 1.57 (0.61,4.07) 7) AOR 1.47 (0.76,2.86) 8) AOR 1.57 (0.61-4.07) 9) AOR 0.62 (0.20,1.98) 10) AOR 1.45 (0.71,2.82)

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

Patient Level Interventions:

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

couples'-based PMTCT intervention compared to standard care. They found no statistically significant difference in PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and evaluated whether conditional cash transfers improved adherence, acceptance of and retention in PMTCT services to 6 weeks postpartum. They found women in the intervention group were significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95% CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.

Patient/Provider Level Interventions:

One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention directed at both patients and providers in which peer mentors were trained to provide in person education sessions for patients. Risk of bias was rated as high or unclear on five of six criteria (Table 2) (31). They found patients in the intervention group were significantly less likely to adhere to ARTs during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-0.74]). No statistically significant effects were found on the remaining outcomes including: ART use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were unable to reach authors for additional information on long term outcomes.

Provider Level Interventions:

Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day PMTCT knowledge and skills training course for nurses and midwives compared to standard training alone (no intervention); risk of bias was rated high or unclear on five of six criteria (Table 2). They found a statistically significant increase in the proportion of women with ART detected in cord blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).

Provider/System Level Interventions:

Five studies reported interventions directed at both the provider and health system level (33,34,35,36,37). Risk of bias ranged from 2 to 5 of six criteria rated as high or unclear (Table 2). Dryden-Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated transmission of HIV test results to clinic staff via short message service (SMS), and ongoing support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring and addressing clinic underperformance). There was a trend towards an increase in the proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.

Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess the impact of two different patient tracing methods routine paper (MIP) and SMS triggered tracing (MIP+SMS) combined with integrated care against standard care (SOC). They found no significant difference in maternal retention in care at 12 months in either intervention group relative to controls using study definitions, or ministry of health definitions for retention. They found no statistically significant difference in infant retention in care at 12 months in either

intervention group relative to controls using study definitions, or ministry of health definitions for retention .

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

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

Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased training of community health workers and increased home visits by community health workers during and post delivery to provide PMTCT counseling and newborn care. They found a significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in mother to child HIV transmission at 12 weeks.

System Level Interventions:

Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias ranged from 2 to 5 of six criteria rated as high or unclear risk of bias (Table 2). Aliyu et al. (38) evaluated an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community involvement through male champions, compared to standard care across 12 clusters and 369 patients. They found significant improvement in the proportion of eligible women 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 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-19.7]).

Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and evaluated the impact of integration of HIV and maternal child health services during both antenatal and postnatal periods. They found no improvement in the proportion of women receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48 hours and the proportion of HIV positive infants.

Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a statistically significant increase in the proportion of eligible women receiving ARTs during pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).

Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during pregnancy and post-delivery. They found statistically significant improvements in maternal antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks (RR= 1.08 [1.00-1.16]).

Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was a no significant difference in maternal AZT/HAART use prior to labor, during labor, maternal NVP/HAART use at onset of labor, and infant 6 week HIV testing relative to controls.

Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters in 3 countries, including 1876 patients. They found no significant improvement in the proportion of pregnant women receiving ARTs.

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

Discussion:

Eighteen studies were included in our review. Heterogeneity of interventions and outcome reported limited both comparison across studies and intervention categories, as well as, opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias, primarily due to limitations inherent to health systems research and unclear reporting of key methodological factors.

Based on our review findings, several interventions appear promising. In the single meta-analysis conducted with data from two studies (25,26), we found a significant increase in ART use during pregnancy with integration of HIV and antenatal care compared to standard non-integrated care. Consistent with the findings of our meta-analysis, narrative review of three

studies found small positive effects of integration of HIV and antenatal care, alone or as part of a complex intervention, on ART use during pregnancy. Four studies evaluating different approaches to outreach services alone or in combination with other interventions found small positive effects on linkage to care, ART use during pregnancy and labor/delivery, and early infant HIV testing. Two studies found positive effects of role expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy and, when combined with outreach services, positive effects were seen on long term retention in care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT outcomes, each in a single study, included: educational meetings, conditional cash transfers, continuous quality improvement, and use of information and communication technology.

In keeping with other systematic reviews focused on interventions aimed at improving PMTCT care and outcomes published to date (8,9,13,14,15), our review found the evidence base available to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor Car et al. (9), which included a single study and found improved ART use in labor/delivery from integration of care, our single meta-analysis including 2 studies found a positive effect of integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only 2 of which met inclusion criteria for the present review, and they also found variable effects of non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al. (14) included 10 articles, with 2 overlapping studies included in our review, and focused on postpartum retention of women in PMTCT and ART care. This latter review, which included both high and LMICs and a broader range of study designs, focused on a limited portion of the PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone

interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to improve PMTCT service delivery and promote retention. Their review was conducted over a similar timeframe to the present review, however, it differs from the present review in its inclusion of high income country studies, inclusion of a range of study designs, and in its approach to categorization of interventions. Thirty-four studies were included in their review, 11 of which were included in the present review. They found weak evidence for improvement of early infant HIV diagnosis from mobile-phone based interventions and for male involvement in reducing infant HIV transmission.

Given the focus of the present review on providing evidence-based guidance to PMTCT program planners and implementers based LMICs our review differs from the reviews noted above in several ways. First, to optimize the quality of evidence we limited our review to randomized and non-randomized controlled trials and interrupted times series studies. Second, to increase the applicability of findings to LMIC implementers, we limited our review to studies conducted in LMICs. Third, we included a broad range of intervention categories and included both maternal and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to provide information of direct relevance to implementation planning, we categorized and analyzed interventions at both the level at which they are implemented (patient, provider, system) and using the EPOC intervention classification scheme, which groups interventions based on the intervention process/activities employed.

Limitations:

While agreement on data extraction was not calculated, an initial calibration exercise was carried out to ensure consistency in data extraction. Following this, comparison of completed data extraction forms revealed few differences. Although no study was excluded for language, it is

possible that use of translation software may have resulted in exclusion of an eligible study due to inaccurate translation. Additionally, while unlikely to have led to a significant difference in results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO as the later was not accessible to the second information technologist.

The multifaceted nature of the majority of interventions evaluated and variability in PMTCT outcomes reported, limited our ability to combine studies statistically. In addition, efforts to contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due to the small number of included studies publication bias could not be examined. Additionally, although pre-specified in our protocol, interpretation of findings, most commonly infant HIV infection rates, are limited by lack of power to assess secondary outcomes among included studies. Finally, as 7 of the 18 studies limited participation to women 17-18 years of age or older, results may be less generalizable to younger mothers.

Future Directions:

Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were generally small and often mixed across studies, and based on a small number of studies that were largely at moderate to high risk of bias. Further research is needed both to improve quantity and quality of data. First, replication of promising approaches is needed. Second, improved publication reporting to ensure key methodological factors are addressed and to provide detail on the likely impact of factors that cannot be modified through design. This transparency in reporting will enhance interpretation and utility of findings in informing PMTCT policy and program decision making. For example, while the nature of designs for evaluating PMTCT

interventions, often make blinding of participants impossible, description of the context and likely impact would aid interpretation. Additionally, use of blinded outcome assessment or objective outcomes such as laboratory confirmation of ART in blood samples will increase study impact. Third, given the inherent difficulties in evaluating complex interventions, increased use of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade where feasible, would allow for increased comparison across interventions.

Conclusions:

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

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

MeSH: Medical Subject Headings; MOH: Ministry of Health; NVP: Nevirapine, PMTCT: Prevention of mother to child transmission of HIV; RCT: Randomized controlled trial; SMS: Short message service; SOC: Standard care; Versus: vs.

Declarations:

Ethics approval and consent to participate: Not applicable.

Consent for publications: Not applicable.

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***Authors' contributions*:** LPR and MvL conceived the study. LPR and SS developed the search strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence tables and manuscript. LPR conducted the meta-analysis with support from BP. MCH, NER, SP, ML, and FC provided content expertise and assisted with preparation of the protocol and manuscript. All authors provided critical revision of the manuscript and read and approved the final manuscript.

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Captions for appended Figures:

Figure 1: PRISMA diagram of search results and screening

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

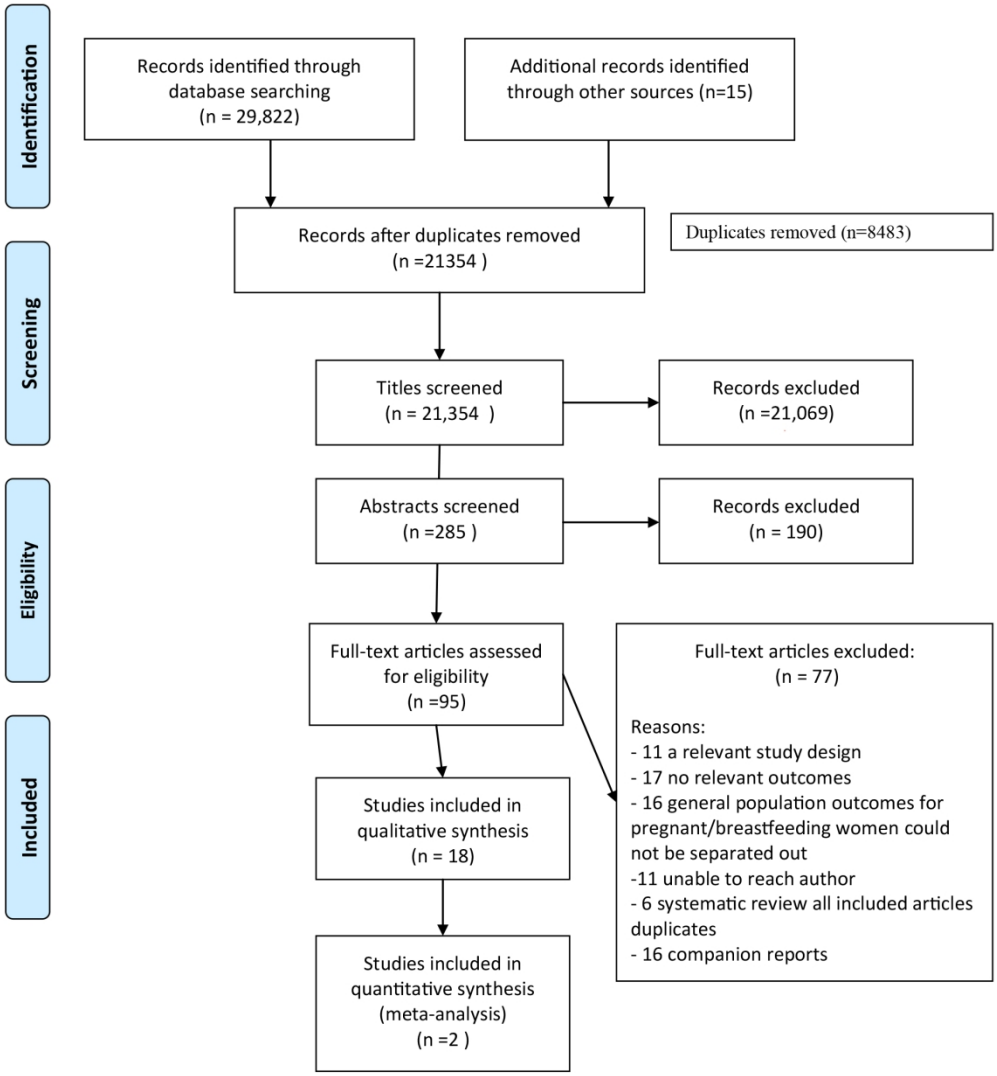

Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

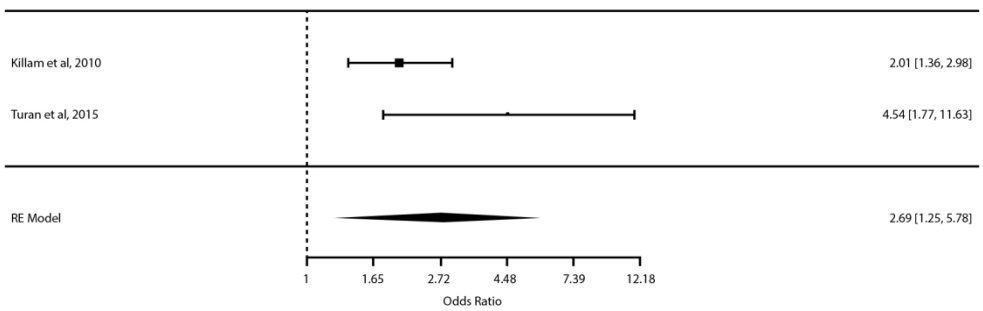

Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)

Appendix A: Search Strategy Ovid MEDLINE(R) <1946 to June Week 2 2018>:

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)

34 (breast adj2 fed*).tw,kw,kf. (5276)
35 in-utero.tw,kw,kf. (20490)
36 (intrauterine or intra-uterine).tw,kw,kf. (42420)
37 (trans-placent* or transplacent*).tw,kw,kf. (5212)
38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)
39 (parent* adj2 (child* or infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (28605)
40 mother*.tw,kw,kf. (147803)
41 (nursing adj2 (infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (1319)
42 (prenatal* or pre-natal*).tw,kw,kf. (70920)
43 (perinatal* or peri-natal*).tw,kw,kf. (51747)
44 (post-natal* or postnatal*).tw,kw,kf. (85370)
45 (antenatal* or antenatal*).tw,kw,kf. (23135)
46 (antepartum* or ante-partum*).tw,kw,kf. (4566)
47 (postpartum* or post-partum*).tw,kw,kf. (40829)
48 maternal*.tw,kw,kf. (172644)
49 or/1-48 (1763167)

HIV/AIDS

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)

68 (aids adj1 related).tw,kw,kf. (6614)
69 htlv*.tw,kw,kf. (11427)
70 hiv##.mp,kw,kf. (1760)
71 or/50-70 (325026)

Patient uptake / dropouts / participation
72 Patient Dropouts/ (6786)
73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)
74 exp Consumer Participation/ (32566)
75 dropout*.tw,kw,kf. (6483)
76 (uptake or up-take).tw,kw,kf. (248330)
77 (drop* adj1 out$1).tw,kw,kf. (8228)
78 (refusal* or refuse$1 or refusing).tw,kw,kf. (23366)
79 (patient* adj2 (elope or elope$1 or eloping)).tw,kw,kf. (4)
80 (non complian* or noncomplian*).tw,kw,kf. (9990)
81 complian*.tw,kw,kf. (84306)
82 (uncooperat* or unco-operat* or un-co-operat*).tw,kw,kf. (1028)
83 (cooperat* or co-operat*).tw,kw,kf. (102475)
84 (non-accept* or nonaccept*).tw,kw,kf. (592)
85 accept*.tw,kw,kf. (279089)
86 (nonparticipat* or non-participat*).tw,kw,kf. (1298)
87 participat*.tw,kw,kf. (322007)
88 (nonadher* or non-adher*).tw,kw,kf. (10638)
89 adher*.tw,kw,kf. (114637)
90 (retain* or retention*).tw,kw,kf. (244370)
91 (non-attend* or nonattend*).tw,kw,kf. (1453)
92 attend*.tw,kw,kf. (110407)
93 (comply* or complies or complian*).tw,kw,kf. (91550)
94 (non-comply* or noncomply* or non-complian* or noncomplian*).tw,kw,kf. (10004)
95 reluctan*.tw,kw,kf. (8504)
96 ((healthcare or care or advice or medical or information) adj3 seek$3).tw,kw,kf. (15252)
97 (disengag* or dis-engag*).tw,kw,kf. (2812)
98 engag*.tw,kw,kf. (82419)
99 avoid*.tw,kw,kf. (237366)
100 ut.fs. (144195)
101 ignor*.tw,kw,kf. (27215)
102 reject*.tw,kw,kf. (82472)

103 (non-embrac* or nonembrac*).tw,kw,kf. (0)
104 (un-embrac* or unembrac*).tw,kw,kf. (1)
105 (embrace* or embracing).tw,kw,kf. (7691)
106 (un-accept* or unaccept*).tw,kw,kf. (14546)
107 (unadher* or un-adher*).tw,kw,kf. (14)
108 no-show*.tw,kw,kf. (484)
109 (follow* adj1 up).tw,kw,kf. (638770)
110 incent*.tw,kw,kf. (17823)
111 enabl*.tw,kw,kf. (214935)
112 disincent*.tw,kw,kf. (859)
113 utiliz*.tw,kw,kf. (319558)
114 (inclin* or disinclin*).tw,kw,kf. (12034)
115 or/72-114 (2984236)

Study type / characteristics

116 randomized controlled trial.pt. (387105)
117 exp Randomized controlled trial/ (387132)
118 exp Randomized Controlled Trials as Topic/ (97414)
119 clinical trial.pt. (490674)
120 Double-Blind Method/ (128228)
121 Placebos/ (32662)
122 clinical trials as topic/ (171490)
123 evaluation research/ (119973)
124 program evaluation/ (47548)
125 Feasibility Studies/ (45412)
126 Pilot Projects/ (85700)
127 Evaluation Studies as Topic/ (119973)
128 Cost-Benefit Analysis/ (61646)
129 (random* or non-random* or unrandom* or nonrandom*).mp,kw,kf. (874470)
130 placebo*.mp,kw,kf. (168179)
131 rct*1.tw,kw,kf. (17367)
132 ((singl* or doubl* or trebl* or tripl*) adj1 (mask* or blind* or dumm*)).mp,kw,kf. (176744)
133 evaluat*.mp,kw,kf. (2416275)
134 effectiv*.mp,kw,kf. (1149619)
135 sustainab*.mp,kw,kf. (23041)
136 feasib*.mp,kw,kf. (177882)
137 appropriateness.mp,kw,kf. (12458)

138 efficac*.mp,kw,kf. (507876)

139 impact*.mp,kw,kf. (537916)

140 (pilot adj2 (project* or study or studies)).mp,kw,kf. (103303)

141 cost-effectiv*.mp,kw,kf. (73309)

142 (cost*1 adj2 benefit*1).mp,kw,kf. (69472)

143 (interrupt* adj2 time).mp,kw,kf. (1224)

144 or/116-143 (4705604)

Lower middle income countries

145 Developing Countries/ (63034)

146 (lmic or lmics or lami countr*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)

147 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)

148 (Afghan* or Albania* or Algeria* or Angola* or Antigua* or Barbud* or Argentin* or Armenia* or Aruba* or Azerbaijan* or Bahrain* or Bangladesh* or Barbad* or Benin* or Byelarus* or Byelorus* or Belarus* or Belorus* or Beliz* or Bhutan* or Bolivia* or Bosnia* or Herzegovin* or Hercegovin* or Botswan* or Brasil* or Brazil* or Bulgaria* or Burkina Faso* or Burkina Fasso* or Upper Volta* or Burundi* or Urundi* or Cambodia* or Khmer Republic or Kampuchea* or Cameroon* or Cameron* or Cape Verde* or Central African Republic or Chad* or Chile* or China or chinese or Colombia* or Comoros* or Comoro Islands or Comores or Mayott* or Congo* or Zair* or Costa Rica* or Cote d'Ivoire or Ivory Coast or Croatia* or Cuba* or Cyprus or cyprian or Czechoslovakia* or Czech Republic or Slovakia* or Slovak Republic or Djibouti* or French Somaliland or Dominica* or East Timor or East Timur or Timor Leste or Ecuador* or Egypt* or United Arab Republic or El Salvador* or Eritrea* or Estonia* or Ethiopia* or Fiji* or Gabon* or Gambia* or Gaza* or Georgia Republic or Georgian Republic or georgian or Ghana* or Gold Coast or Greece or greek or Grenada* or Guatemala* or Guinea* or Guam* or Guiana* or Guyana* or Haiti* or Hondura* or Hungar* or India* or Maldiv* or Indonesia* or Iran* or Iraq* or Isle of Man or Jamaica* or Jordan* or Kazakh* or Kenya* or Kiribati* or Korea* or Kosovo* or Kyrgyz* or Kirghiz* or Kirgiz* or Lao PDR or Laos* or Latvia* or Leban* or Lesotho* or Basutoland or Liberia* or Libya* or Lithuania* or Macedonia* or Madagascar* or Malagasy Republic or Malay* or Sabah* or Sarawak* or Malawi* or Nyasaland* or Mali* or Malta* or Marshall Island* or Maurit* or Agalega Island* or Mexic* or Micronesia* or Middle East* or Moldova* or Moldovia* or Mongolia* or Montenegr* or Morocc* or Ifni* or Mozambiq* or Myanmar* or Myanma or Burma* or Namibia* or Nepal* or Netherlands Antill* or New Caledonia* or Nicaragua* or Niger* or Northern Mariana Island* or Oman* or Muscat* or Pakistan* or Palau* or Palestin* or Panama* or Paragua* or Peru* or Phi?lippin* or Poland or polish or Portug* or Puerto Ric* or Romania* or Rumania* or

Roumania* or Russia* or Rwanda* or Ruanda* or Saint Kitts* or St Kitts or Nevis* or Saint Lucia* or St Lucia* or Saint Vincent* or St Vincent* or Grenadin* or Samoa* or Navigator Island* or Sao Tome* or Saudi Arabia* or saudi or Senegal* or Serbia* or Montenegr* or Seychelles or Sierra Leone or Slovenia* or Sri Lanka* or Ceylon* or Solomon Islands or Somalia* or South Africa* or Sudan* or Surinam* or Swaziland or swazi or Syria* or Tajik* or Tadjik* or Tadzhik* or Tanzania* or Thailand or thai or Togo or Togolese Republic or Tonga* or Trinidad* or Tobag* or Tunisia* or Turkey or turkish or Turkmenistan* or Turkmen* or Uganda* or Ukrain* or Urugua* or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbek* or Vanuat* or New Hebrides or Venezuela* or Vietnam* or Viet Nam* or West Bank or Yemen* or Yugoslavia* or Zambia* or Zimbabw* or Rhodesia* or cabo verd*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)

149 or/145-148 (4677916)

Full topic

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

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

Full topic minus animal-only studies

152 150 not 151 (3291)

****

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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 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 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 Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 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
DISCUSSION			
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
FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

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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

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS
Keywords:	HIV, prevention of mother to child transmission, interventions, uptake, retention

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

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Word Count: (4098)

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:

The evidence on effectiveness of interventions to improve uptake and retention of mothers and infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal care may improve ART use during pregnancy. Future studies to replicate promising approaches are needed. Improved reporting of key methodological criteria will facilitate interpretation of findings and improve the utility of evidence to PMTCT program planners.

Systematic review registration: PROSPERO-CRD42015020829

Key Words: HIV, prevention of mother to child transmission, interventions, retention, uptake

Strengths and Limitations of this review:

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

Introduction:

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

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

of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of included studies reported PMTCT outcomes, this was not a primary focus of the review. A second review focused on postpartum retention of women in PMTCT and ART care (14). This review focused on a limited portion of the PMTCT cascade. A third review (15) focused on interventions to improve PMTCT service delivery and promote retention. This review included a range of study designs and studies conducted in both high and low-middle income countries and as such, is of less value as a guide to decision making for PMTCT policy and programming in LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by: lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high income country studies where the context of PMTCT care is often substantially different than in LMICs.

This review was developed in collaboration with knowledge users from the Malawi Ministry of Health's HIV treatment and care technical working group. The objective of this current review was to identify what interventions at the patient, provider, or health system level are effective compared to no intervention or usual care in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health services in LMICs, this review is targeted to provide guidance for PMTCT policy and programming in LMICs, and therefore included a broad range of intervention categories, as well as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.

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). 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

results could be abstracted. No restriction was placed based on language of publication, publication status, study time frame, or duration of follow-up.

Information Sources and Literature Search:

A search strategy was developed in consultation with an experienced information specialist (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review of Electronic Search Strategies checklist (22). The following databases were searched from inception to July 31, 2015 and subsequently updated using the same search strategy for the period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV, pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science, Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE, ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library, WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov. Several databases planned for inclusion in our search were no longer available or not accessible by our group at the time of the search and were therefore not included: AIDS Education Global Information System, British Library Catalogue, and the New York Academy of Grey Literature. In addition, we searched reference lists of included articles, and contacted several experts in the field to inquire about eligible unpublished or in progress studies. See supplementary file for complete MEDLINE search strategy.

Study Selection and Data Collection Process:

A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement. Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then abstracts were screened, and second, the full-text articles were screened. Translation software was utilized to screen articles at the titles and abstracts level, with no non-English articles remaining at the full article review phase. A data abstraction form was created using the EPOC data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in screening and data extraction. A calibration exercise was conducted with completed data extraction forms compared and discussed for each of the first 3 articles to ensure consistency; data extraction was then completed for the remaining articles independently and in duplicate by 2 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each study included: population, intervention, comparator, context, outcomes, study design, time frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment, percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis, and percentage of women and infants retained in PMTCT care/completing the ART regimen as defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants completing post-exposure HIV testing 6 weeks following termination of breast feeding for all infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV; adverse events; major or minor congenital malformations; small for gestational age; pre-mature delivery; still birth; and infant death within first 2 years of life (18).

When necessary to clarify published data or to obtain unpublished data, we contacted primary authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions, and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to calculate risk ratios were not available in the publication. Three responded and provided the requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional data as they were submitting the manuscript for publication.

Methodological Quality/Risk of Bias Appraisal:

Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies included in the meta-analysis, risk of publication bias could not be examined using funnel plots. Selective reporting bias was assessed through review of trial registrations where available and categorized as unclear if not registered.

Data Synthesis:

Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy for health system interventions and discrepancies resolved through discussion (23). Clinical heterogeneity was determined based on patient, intervention, and outcome characteristics. Descriptive synthesis of study results were conducted for all studies, and are reported narratively and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate intervention effects using the Metafor Package in the statistical software R (24). Statistical heterogeneity was examined using the I^2 statistic, with $I^2 \geq 75\%$ indicating significant heterogeneity (16).

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).

Study Characteristics:

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

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 ≥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 • Maternal age (mean): I = 29.3, C = 29.7	1) ART during pregnancy 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 ≥18 and at least 32 weeks gestation	PMTCT providers trained to prepare and counsel women on how to store and	Usual care	• Self-management • 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 478 couples	• % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive • Maternal age (mean): I = 28.3; C = 28.1	1) ART detected in mother blood samples at birth 2) ART detected in infants blood at birth 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 2) Uptake of PMTCT services through to 6 weeks postpartum 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 • Education	8 Clusters 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) 2) ART during labor (AZT or HAART 3) NVP or HAART during labor 4) Infant NVP at birth 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 2444 Patients	% HIV positive at enrollment: 33% overall	NVP in cord blood
Dryden-Peterson; 2015	Provider/System	Stepwedge 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 • Educational meetings	19 Clusters 336 women	% HIV positive: I = 189 (47.6%) and C= 177 (44.6%) • Maternal age (median): (I = 28; C = 29	ART initiation by 30 wks gestation

Mwapasa; 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 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 • The use of information and communication technology	30 Clusters 1350 women	• Maternal age (median): MIP = 29.5; MIP+SMS = 29.2; SOC = 29.4	1) Maternal retention in care at 12 months postpartum trial data 2) Infant retention in care at 12 months postpartum trial data 3) Maternal retention in care at 12 months using MOH definition 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	• Continuous quality improvement	32 Clusters: (6 later excluded) 532 women (21 withdrew leaving 511 in total)	• Maternal age (median): I = 27 ; C = 27	1) ART initiated within 2 week of enrolment 2) Retention in care at 6 months 3) Infants starting prophylaxis within 72 hours 4) infant HIV testing at 6-10 weeks
Phiri; 2017	Provider/System	3 Arm, Cluster RCT	Malawi (SE, SW and Central West	Pregnant and breastfee	FBPS - women received SOC and met with	SOC = standard of care facilities provided	• Role expansion or task shifting outreach	21 Clusters 1269 women	• Maternal age (median across all 3	1) ART uptake 2) Retained 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 • The use of information and communication technology		arms): 27	care at 1 year: 3) Retained in care at 2 years trial data 4) Retained in care at 2 years MOH definition 5) Infant HIV tested at 6 weeks 6) Infant HIV-positive at 6 weeks

					within 1 week of a missed clinic visit.					
Tomlinson; 2014	Provider/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 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.	• Role expansion or task shifting • Outreach services	30 Clusters 3957 women	Maternal age (median): I = 23; C = 23	1) Infant HIV testing by 6 weeks 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 HIV status but had never received treatment	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 partner) participation, and community involvement (male community peer champions providing	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.	• Role expansion/ task shifting Integration • Packages of care	12 Clusters 369 patients	• Maternal age (median): I = 26 ; C = 28	1) Maternal ART initiation 2) Maternal-infant retention in care at 6 week postpartum 3) Maternal-infant retention in care at 12 weeks post 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	• Integration • Educational meetings	6 Clusters	Not available	1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 3) Infant HIV-positive
Killam; 2010	System	Stepwedge 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	• Integration	8 Clusters 31536 patients	• % HIV positive: I = 21.8%; C = 22.2% • Maternal age (mean): I = 27.5; C = 27.3	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	• The use of information and communication technology	388 Patients	• % HIV positive: 29.3% (388/1324) • 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+)	1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks
Rotheram-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	• Role expansion or task shifting • Outreach services	26 Clusters: (2 later removed); 1144 eligible women	• %HIV positive: I = 149 (25.5%); C =146 (26.7%) • Mean maternal age : I = 26.5; C = 26.3	1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART

										at onset of labor 4) Infant prophyl axis within 24 hours of birth 5) AZT dispens ed for infant and medicat ed as prescrib ed 6) Infant HIV test at 6 weeks
Rustagi ; 2016	System	Cluste r RCT	Cote d'Ivoire, Kenya, Mozambi que	Public and non-profit health facilities with PMTCT services. Pregnant women presentin g for antenatal care	A five-step, facility-level systems analysis and improveme nt interventio n designed to maximize effectivene ss of PMTCT service delivery by improving understand ing of inefficienci es	Usual care	• Continuou s quality improvem ent	36 Clusters 1876 patients	Not available	1) ART in pregnan cy 2) Infants HIV tested by 6-8 weeks
Turan; 2015	System	Cluste r 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-integrate d ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women to a separate HIV clinic at the same facility	• Integration	12 Clusters: 1172 women	• %HIV positive: I = 48.5%, C = 51.5% • Maternal age (mean): I = 25.0, C = 24.8	1) ART during pregnan cy 2) ART during Labor 3) ART after birth 4) Infant ART after 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

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

Reporting of population characteristics varied widely across studies as did outcome definitions. Seven studies limited participation to pregnant women 17-18 years of age or older; median ages

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

Reported outcomes varied substantially across studies, with few studies within intervention categories reporting comparable outcomes. For example, 5 studies reported interventions employing integration alone [2] or in combination with other interventions [3], with only 1 PMTCT outcome in common among the 2 studies employing integration alone. The most commonly reported outcomes were maternal ART use during pregnancy and labor and delivery, infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.

As a result of the multifaceted nature of the majority of interventions employed, and variability in PMTCT outcomes reported, the ability to combine results statistically was limited.

Methodological Quality:

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

of participants/personnel (18/18) and blinding of outcome assessment (16/18) (The complete risk of bias table is included as an additional file).

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

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

Descriptive Synthesis:

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

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	• Self-management • 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%) 2) ART detected in infants blood at birth: 12/13 (92%) 3) Infant HIV positive at 6 weeks:1/30 (3.3%)	1) ART detected in mother blood samples at birth: I6/12 (50%) 2) ART detected in infants blood at birth: 9/12 (75%) 3) Infant HIV positive: 3/39 (7.7%)	1) 1.50 (0.78-2.88) 2) 1.23 (0.86-1.77) 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%) 2) Uptake of PMTCT services through to 6 wks postpartum:146/216 (67.6%) 3) HIV positive infants at 6 weeks: 5/169 (3.0%)	1) Retention in care at 6 weeks postpartum: 157/217 (72.4%) 2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%) 3) HIV positive infants at 6 weeks: 6/156 (3.9%)	1) 1.11(1.00-1.23) 2) 1.26(1.08-1.48) 3) 0.77(0.24-2.47)	1) ARD 1.13 (1.02-1.26) 2) ARD 1.31 (1.12-1.54) 3) –
Richter, 2014	Patient/Provider	• Role expansion or task shifting • Educational meetings	Peer Mentor led educational meetings	Usual Care	1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%) 2) ART during labor (AZT or HAART): 282/377 (74.8%); 3) NVP or HAART during labor: 361/377 (95.8%) 4) Infant NVP at birth: 364/377 (96.6%) 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%) 2) ART during labor (AZT or HAART): 334/466 (71.7%) 3) NVP or HAART during labor: 456/466 (97.9%) 4) Infant NVP at birth: 451/466 (96.8%) 5) AZT dispensed for infant and medicated as prescribed: 374/466	1) 0.92 (0.89-0.96) 2) 1.04 (0.96-1.13) 3) 0.98 (0.95-1.00) 4) 1.00 (0.97-1.02) 5) 1.15 (1.09-1.21)	1) AOR 0.44 (0.26,0.74) 2) AOR 1.16(0.44, 3.02) 3) AOR 0.53 (0.20, 1.41) 4) AOR 1.00 (0.36, 2.79) 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-Peterson; 2015	Provider/System	• The use of information and communication technology	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					
Mwapasa; 2017	Provider/System	• Integration • The use of information and communication technology	MIP= integration of antenatal and HIV care, routine patient tracing 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% MIP+SMS 115/493 2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3% MIP+SMS 82/399, 20.1% 3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4% MIP+SMS 332/493, 67%. 4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4% MIP+SMS 323/399, 80.9%	1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7% 2) Infant retention in care at 12 months postpartum trial data: SOC 32/300,10.7 3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1% 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) 2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82) 3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06) 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) 2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31) 3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05) 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/System	• Continuous quality improvement	QI teams established, coaching, and collaborative meetings	Routine MOH support	1) ART initiated within 2 week of enrolment: 261/264 = 98.9% 2) Retention in care at 6 months. 117/264 = 44.3% 3) Infants starting prophylaxis within 72 hours : 138/209 = 66**%** 4) Infant HIV testing at 6-10 weeks 102/209 = 48.8%;	1) ART initiated within 2 week of enrolment: 233/247 = 94.3% 2) Retention in care at 6 months. 102/247 = 41.3% 3) Infants starting prophylaxis within 72 hours 145/194 = 74.7% 4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%	1) 1.05 (1.01-1.08) 2) 1.07 (0.88-1.31) 3) 0.88 (0.78-1.00) 4) 1.93 (1.46-2.55)	1) -- 2) ARR 1.08(0.78, 1.49) 3) ARR 0.95 (0.84, 1.07) 4) ARR 1.76(1.27, 2.42)
Phiri; 2017	Provider/System	• Role expansion or task shifting outreach services • The use of information and communication technology	FBPS – facility based peer support from mentor mothers CBPS- community based peer support from	SOC- standard of care	1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%) 2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%) 3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394	1) ART uptake: SOC- 361/447(81%) 2) Retained in care at 1 year: SOC- 261/361 (74%) 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) 2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10) 3) SOC vs FBPS 1.38(1.19-	1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18) 2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20) 3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30) 4) --

			mentor mothers		(54%) 4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%) 5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%) 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%) 5) Infant HIV test at 6 weeks: SOC- 169/273(62%) 6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)	1.60), SOC vs CBPS 1.42 (1.22-1.65) 4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43) 5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38) 6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09)	5) -- 6) ---
Tomlinson: 2014	Provider/System	• Role expansion or task shifting • Outreach services	10 structured home visits from community health workers addressing PMTCT and newborn care	3 home visits from community health workers providing support in accessing social welfare grants	1) Infant HIV testing by 6 weeks: 420/571(73.6%) 2) Infant HIV positive at 12 weeks: 28/568 (4.9%)	1) Infant HIV testing by 6 weeks: 465/698(66.6%) 2) Infant HIV positive at 12 weeks: 32/697 (4.6%)	1) 1.10 (1.03-1.19) 2) 1.07 (0.65-1.76)	1) ARR 1.10 (0.97, 1.25) 2) ARR 1.07 (0.69,1.66)
Aliyu; 2016	System	• Role expansion /task shifting Integration • Packages of care	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%) 3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)	1) Maternal ART initiation for PMTCT: 77/197 (39%), 2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%) 3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%)	1) 2.47 (2.07-2.95) 2) 9.44 (5.60-15.40) 3) 11.40 (6.40-20.34)	1) ARR 3.3 (1.4-7.8) 2) ARR 9.1 (5.2-15.9) 3) ARR 10.3(5.4-19.7)
Geelhoed; 2013	System	• Integration • Educational meetings	Integrated maternal child health and HIV care	Usual Non-integrated care	1) ART in labor: post intervention:112/121 (93%) 2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%); 3) Infants HIV-positive: post intervention: 9/123 (7%)	1) ART in labor: intervention phase =93/96(97%) 2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%) 3) Infants HIV positive: intervention phase: 7/60(12%)	1) 0.96 (0.90-1.02) 2) 0.93 (0.88-0.97) 3) 0.63 (0.25-1.60)	-- -- --
Killam; 2010	System	• Integration	Integration of antenatal	Usual non-integrat	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%) 2) Infant HIV testing by 8 wks: I172/187 (92.0%)	1) Maternal postpartum clinic attendance: 22/187 (11.8%) 2) Infant HIV testing by 8 wks: 154/181 (85.1%)	1) 1.66 (1.03-2.70) 2) 1.08 (1.00-1.16)	-- -
Rotheram-Borus; 2014	System	• Role expansion or task shifting • Outreach services	Antenatal and postnatal home visits from community health workers	Usual care	1) ART prior to labor: 169/179 (94.4%) 2) AZT or HAART during labor: I164/179 (91.6%) 3) NVP or HAART at onset of labor: 166/179 (92.7%) 4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%) 5) Infant ART after birth: 172/179 (96.1%) 6) Infant HIV testing at 6 weeks: 155/160 (96.9%)	1) ART prior to labor: 149/159 (93.7%) 2) AZT or HAART during labor: 147/159 (92.5%) 3) NVP or HAART at onset of labor: 142/159 (89.3%) 4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%) 5) Infant ART after birth: 142/159 (89.3%) 6) Infant HIV testing at 6 weeks: 132/140 (94.3%)	1) 1.01 (0.95-1.06) 2) 0.99 (0.93-1.06) 3) 1.04 (0.97-1.11) 4) 1.08 (1.01-1.15) 5) 1.08 (1.01-1.14) 6) 1.03 (0.98-1.08)	1) AOR 1.08 (0.42, 2.80) 2) AOR 0.87 (0.39, 1.95) 3) AOR 1.52(0.70, 3.31) 4) AOR 2.94(1.41, 6.12) 5) AOR 2.95 (1.12, 7.73) 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%) 2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)	1) ART in pregnancy: 664/1037(64%) 2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)	1) 1.07 (1.00-1.14) 2) 1.23 (1.09-1.40)	-- --
Turan; 2015	System	• Integration	Integrated HIV and antenatal care	Usual, non-integrated care	1) ART during pregnancy: 138/173 (80%) 2) ART during Labor: 28/173 (16%) 3) ART after birth: 22/173 (13%) 4) Infant ART after birth: 50/173 (29%) 5) ART throughout all 3 PMTCT periods: 37/176 (21.0%) 6) Infant HIV testing before 3 months: 143/569 (25%) 7) Infant HIV testing at 9 months: 361/569 (63%) 8) Infants HIV tested by 6 weeks: 143/568 (25%) 9) Infants HIV positive at 6	1) ART during pregnancy: 75/152 (49%) 2) ART during Labor: 84/152 (55%) 3) ART after birth: 57/152 (38%) 4) Infant ART after birth: 106/152 (70%) 5) ART throughout all 3 PMTCT periods: 23/153 (15.0%) 6) Infant HIV testing before 3 months: 106/603 (18%) 7) Infant HIV testing at 9 months: 326/603 (54%) 8) Infants HIV tested by 6 weeks: 106/594 (18%) 9) Infants HIV positive at 6	1) 1.61 (1.35-1.93) 2) 0.29 (0.20-0.42) 3) 0.34 (0.22-0.53) 4) 0.41 (0.32-0.54) 5) 1.40 (0.87-2.24) 6) 1.43 (1.14-1.79) 7) 1.17 (1.07-1.29) 8) 1.41 (1.13-1.76) 9) 0.64 (0.22-1.84)	1) AOR 4.05 (2.0, 8.0) 2) AOR 0.16 (0.04, 0.68) 3) AOR 0.24 (0.08, 0.70) 4) AOR 0.18 (0.09, 0.35) 5) AOR 1.72 (0.85, 3.48) 6) AOR 1.57 (0.61,4.07) 7) AOR 1.47 (0.76,2.86) 8) AOR 1.57 (0.61-4.07) 9) AOR 0.62 (0.20,1.98) 10) AOR 1.45 (0.71,2.82)

					weeks: I6/143 (4.2%) 10) Infants HIV tested by end of study (up to 12 m): 382/568 (67.3%) 11) Infants HIV positive at 9 months: 28/382 (7.3%)	weeks: 7/106 (6.6%) 10) Infants HIV tested by end of study (up to 12 m): 338/594 (57.0%) 11) Infants HIV positive at 9 months: 27/338 (8.0%)	10) 1.18 (1.08-1.29) 11) 0.92 (0.55-1.53)	11) AOR 0.89 (0.56,1.43)

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

Synthesis of findings according to intervention type and target:

Patient Level Interventions:

Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of bias ranged from 3 to 6 of 6 criteria rated as high or unclear. Ezeanolue et al. (27) included 40 clusters and 3,024 patients and evaluated a complex intervention that included monthly baby showers at participating churches where expectant mothers participated in educational games, received 'mama packs' containing supplies needed during delivery (sterile gloves, alcohol swabs, clean razor, etc.) and laboratory testing, and were given a contact point for follow-up. Women in the intervention group were found to be significantly more likely to complete linkage to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided

pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT intervention compared to standard care. They found no statistically significant difference in PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and evaluated whether conditional cash transfers improved adherence, acceptance of and retention in PMTCT services to 6 weeks postpartum. They found women in the intervention group were significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95% CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.

Patient/Provider Level Interventions:

One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention directed at both patients and providers in which peer mentors were trained to provide in person education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31). They found patients in the intervention group were significantly less likely to adhere to ARTs during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-0.74]). No statistically significant effects were found on the remaining outcomes including: ART use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were unable to reach authors for additional information on long term outcomes.

Provider Level Interventions:

Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day PMTCT knowledge and skills training course for nurses and midwives compared to standard training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They found a statistically significant increase in the proportion of women with ART detected in cord blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).

Provider/System Level Interventions:

Five studies reported interventions directed at both the provider and health system level (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated transmission of HIV test results to clinic staff via short message service (SMS), and ongoing support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring and addressing clinic underperformance). There was a trend towards an increase in the proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.

Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing (MIP+SMS) combined with integrated care against standard care (SOC). They found no significant difference in maternal retention in care at 12 months in either intervention group relative to controls using study definitions, or ministry of health definitions for retention. They found no statistically significant difference in infant retention in care at 12 months in either

intervention group relative to controls using study definitions, or ministry of health definitions for retention .

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

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

Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased training of community health workers and increased home visits by community health workers during and post delivery to provide PMTCT counselling and newborn care. They found a significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in mother to child HIV transmission at 12 weeks.

System Level Interventions:

Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community involvement through male champions, compared to standard care across 12 clusters and 369 patients. They found significant improvement in the proportion of eligible women 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 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-19.7]).

Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and evaluated the impact of integration of HIV and maternal child health services during both antenatal and postnatal periods. They found no improvement in the proportion of women

receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48 hours and the proportion of HIV positive infants.

Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a statistically significant increase in the proportion of eligible women receiving ARTs during pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).

Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during pregnancy and post-delivery. They found statistically significant improvements in maternal antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks (RR= 1.08 [1.00-1.16]).

Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.

Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters in 3 countries, including 1876 patients. They found no significant improvement in the proportion of pregnant women receiving ARTs.

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

Synthesis of findings according to PMTCT outcomes:

The vast majority of studies reported short-term PMTCT outcomes with ART use during pregnancy (10/18) and labor and delivery (6/18), infant prophylaxis at birth (6/18), and infant HIV testing at 6-10 weeks (5/18). Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance. For example, 5 studies found significant improvements in ART use during pregnancy ranging with RR ranging from 1.12 to 2.48 (25, 26, 27, 36, 38), 4 found no significant difference (33, 35, 41, 42) and 1 found significantly reduced ART use

during pregnancy in the control group (31). Findings for ART use during labor and delivery were again mixed, with 4/6 finding no significant effect (29, 31, 39, 41)), 1 finding a significant but small improvement RR=1.17 (32) and 1 finding significantly reduced ART use in the intervention group RR=1.614 (25). Findings for infant prophylaxis at birth and infant HIV testing by 6-10 weeks are similarly mixed. One of 6 studies reported a small significant improvement in infant HIV prophylaxis at birth RR=1.08 (41), 1/6 significantly reduced infant prophylaxis at birth RR=0.41 (25) and 4/6 studies finding no significant difference (28, 31, 35, 39). Three of 6 found significantly improved rates of infant testing by 6-10 weeks of age with RR ranging from 1.08 to 1.93 (35,37,40) and 2/6 no difference (25, 41).

Only 1 study evaluated ART use in the post-partum period and again found a significantly reduced ART use during this period RR=0.34 (25).Two additional studies evaluated uptake across the cascade, with 1/2 finding significantly improved uptake RR= 1.26 (30) and 1/2 finding no difference (25).

Outcome definitions for retention in care and infant HIV-positive rates were highly variable, ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant retention in care at 6 weeks, with 2 studies finding significantly improved retention with RR ranging from 1.11 to 9.44 (30, 38) and the third finding no difference (27).Three studies examined infant HIV-positive rates at 6 weeks post-partum, all found no difference.

Discussion:

Eighteen studies were included in our review. Heterogeneity of interventions and outcome reported limited both comparison across studies and intervention categories, as well as, opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias, primarily due to limitations inherent to health systems research and unclear reporting of key methodological factors.

Based on our review findings, several interventions appear promising. In the single meta-analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use during pregnancy with integration of HIV and antenatal care compared to standard non-integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies found small positive effects of integration of HIV and antenatal care, alone or as part of a complex intervention, on ART use during pregnancy. However, not all studies or all outcomes in some included studies showed significant benefit with integration of ANC and HIV. Therefore, as integrated care is increasingly common future work focusing on how integration of ANC and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes is needed.

Four studies evaluating different approaches to outreach services alone or in combination with other interventions found small positive effects on linkage to care, ART use during pregnancy and labor/delivery, and early infant HIV testing. Two studies found positive effects of role expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy and, when combined with outreach services, positive effects were seen on long term retention in care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT

outcomes, each in a single study, included: educational meetings, conditional cash transfers, continuous quality improvement, and use of information and communication technology.

An important finding of the present review is the high degree of variability in outcome definitions and relative lack of longer-term outcome data. While in some instances variability of outcome definitions may be considered a strength where both self-report and biological markers of ART use are included, variability in timing of outcomes limits comparison across studies and opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is clearly critical to reducing HIV transmission, longer term outcomes are equally important to understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of future work would be substantially improved through both standardization of timing of PMTCT outcomes and through funding opportunities that would allow for evaluation of longer term outcomes.

In keeping with other systematic reviews focused on interventions aimed at improving PMTCT care and outcomes published to date (8,9,13,14,15), our review found the evidence base available to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor Car et al. (9), which included a single study and found improved ART use in labor/delivery from integration of care, our single meta-analysis including 2 studies found a positive effect of integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only 2 of which met inclusion criteria for the present review, and they also found variable effects of non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al.

(14) included 10 articles, with 2 overlapping studies included in our review, and focused on postpartum retention of women in PMTCT and ART care. This latter review, which included both high and LMICs and a broader range of study designs, focused on a limited portion of the PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to improve PMTCT service delivery and promote retention. Their review was conducted over a similar timeframe to the present review, however, it differs from the present review in its inclusion of high income country studies, inclusion of a range of study designs, and in its approach to categorization of interventions. Thirty-four studies were included in their review, 11 of which were included in the present review. They found weak evidence for improvement of early infant HIV diagnosis from mobile-phone based interventions and for male involvement in reducing infant HIV transmission.

Given the focus of the present review on providing evidence-based guidance to PMTCT program planners and implementers based LMICs our review differs from the reviews noted above in several ways. First, to optimize the quality of evidence we limited our review to randomized and non-randomized controlled trials and interrupted times series studies. Second, to increase the applicability of findings to LMIC implementers, we limited our review to studies conducted in LMICs. Third, we included a broad range of intervention categories and included both maternal and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to provide information of direct relevance to implementation planning, we categorized and analyzed interventions at both the level at which they are implemented (patient, provider,

system) and using the EPOC intervention classification scheme, which groups interventions based on the intervention process/activities employed.

Limitations:

While agreement on data extraction was not calculated, an initial calibration exercise was carried out to ensure consistency in data extraction. Following this, comparison of completed data extraction forms revealed few differences. Although no study was excluded for language, it is possible that use of translation software may have resulted in exclusion of an eligible study due to inaccurate translation. Additionally, while unlikely to have led to a significant difference in results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO as the later was not accessible to the second information technologist.

The multifaceted nature of the majority of interventions evaluated and variability in PMTCT outcomes reported, limited our ability to combine studies statistically. In addition, efforts to contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due to the small number of studies included in the meta-analysis publication bias could not be examined. Additionally, although pre-specified in our protocol, interpretation of findings, most commonly infant HIV infection rates, are limited by lack of power to assess secondary outcomes among included studies. As 7 of the 18 studies limited participation to women 17-18 years of age or older, results may be less generalizable to younger mothers. Finally, although the EPOC search filter is designed to identify articles from all low- and middle-income countries, only articles from Sub-Saharan Africa were included in the review. Results therefore may be less

generalizable to LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the evidence to date and where funding should be targeted for future research based on knowledge users needs.

Future Directions:

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

Conclusions:

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

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

Declarations:

Ethics approval and consent to participate: Not applicable.

Consent for publications: Not applicable.

Availability of data and material: No additional data available.

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***Authors' contributions*:** LPR and MvL conceived the study. LPR and SS developed the search strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence tables and manuscript. LPR conducted the meta-analysis with support from BP. MCH, NER, SP, ML, and FC provided content expertise and assisted with preparation of the protocol and manuscript. All authors provided critical revision of the manuscript and read and approved the final manuscript.

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Captions for appended Tables and Figures:

Table 1: Characteristics of Included Studies

Table 2: Results of Included Studies

Figure 1: PRISMA diagram of search results and screening

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

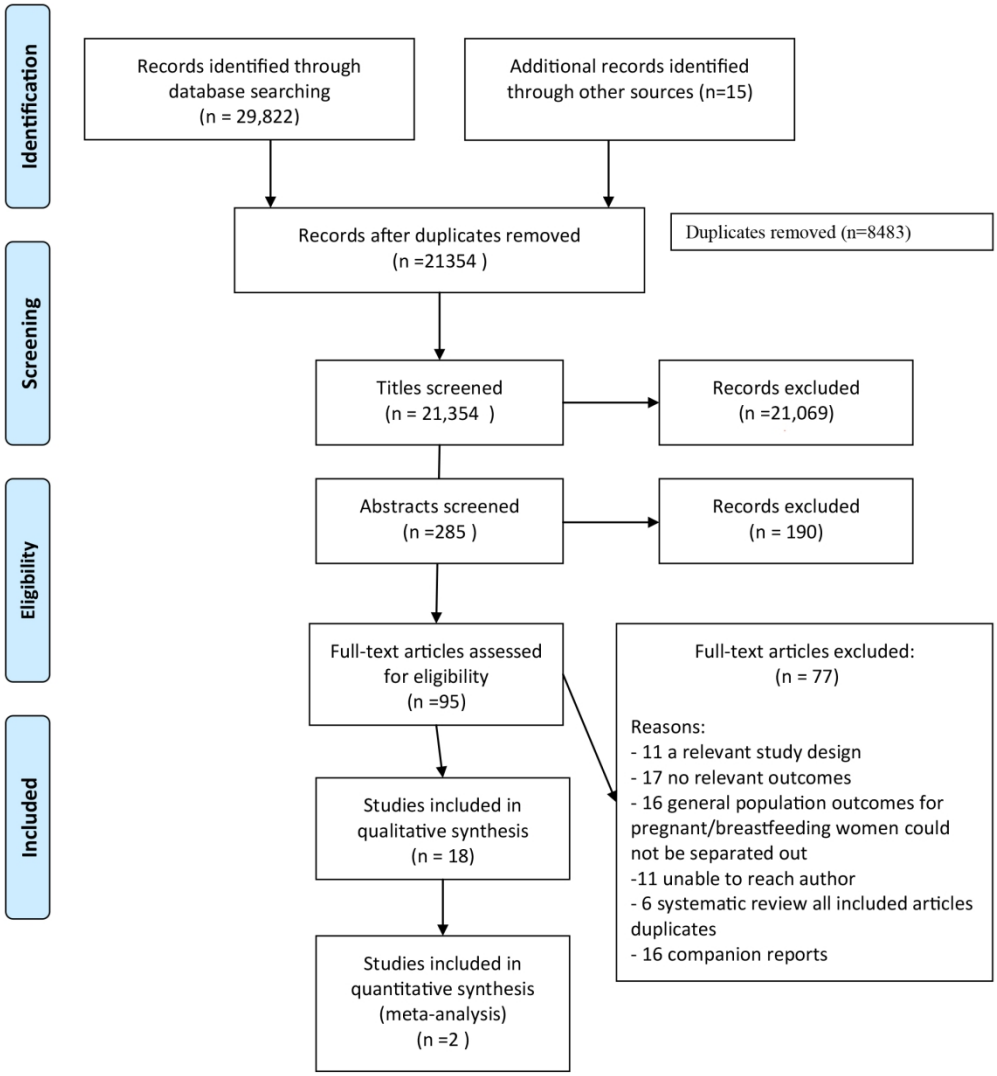


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

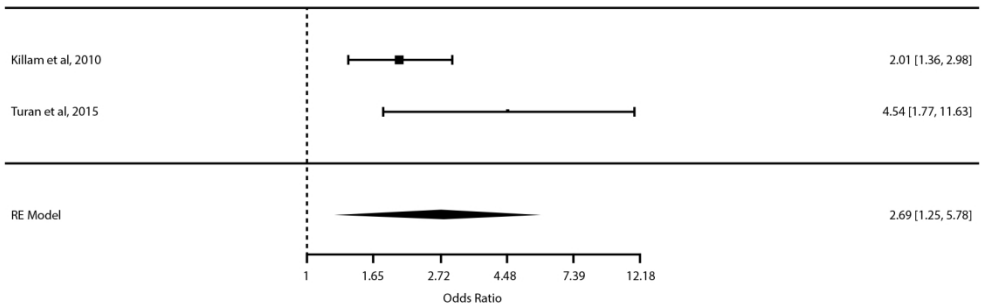
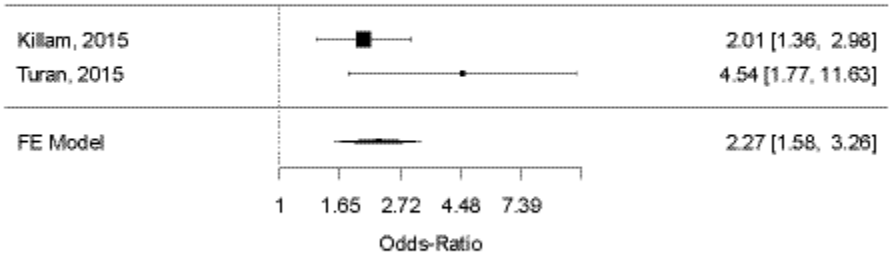


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)


Killam, 2015
Turan, 2015
FE Model
2.01 [1.36, 2.98]
4.54 [1.77, 11.63]
2.27 [1.58, 3.26]
1
1.65
2.72
4.48
7.39
Odds-Ratio

Search Strategy Ovid MEDLINE(R) <1946 to June Week 2 2018>:

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)

34 (breast adj2 fed*).tw,kw,kf. (5276)
35 in-utero.tw,kw,kf. (20490)
36 (intrauterine or intra-uterine).tw,kw,kf. (42420)
37 (trans-placent* or transplacent*).tw,kw,kf. (5212)
38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)
39 (parent* adj2 (child* or infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (28605)
40 mother*.tw,kw,kf. (147803)
41 (nursing adj2 (infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (1319)
42 (prenatal* or pre-natal*).tw,kw,kf. (70920)
43 (perinatal* or peri-natal*).tw,kw,kf. (51747)
44 (post-natal* or postnatal*).tw,kw,kf. (85370)
45 (antenatal* or antenatal*).tw,kw,kf. (23135)
46 (antepartum* or ante-partum*).tw,kw,kf. (4566)
47 (postpartum* or post-partum*).tw,kw,kf. (40829)
48 maternal*.tw,kw,kf. (172644)
49 or/1-48 (1763167)

HIV/AIDS

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)

68 (aids adj1 related).tw,kw,kf. (6614)
69 htlv*.tw,kw,kf. (11427)
70 hiv##.mp,kw,kf. (1760)
71 or/50-70 (325026)

Patient uptake / dropouts / participation
72 Patient Dropouts/ (6786)
73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)
74 exp Consumer Participation/ (32566)
75 dropout*.tw,kw,kf. (6483)
76 (uptake or up-take).tw,kw,kf. (248330)
77 (drop* adj1 out$1).tw,kw,kf. (8228)
78 (refusal* or refuse$1 or refusing).tw,kw,kf. (23366)
79 (patient* adj2 (elope or elope$1 or eloping)).tw,kw,kf. (4)
80 (non complian* or noncomplian*).tw,kw,kf. (9990)
81 complian*.tw,kw,kf. (84306)
82 (uncooperat* or unco-operat* or un-co-operat*).tw,kw,kf. (1028)
83 (cooperat* or co-operat*).tw,kw,kf. (102475)
84 (non-accept* or nonaccept*).tw,kw,kf. (592)
85 accept*.tw,kw,kf. (279089)
86 (nonparticipat* or non-participat*).tw,kw,kf. (1298)
87 participat*.tw,kw,kf. (322007)
88 (nonadher* or non-adher*).tw,kw,kf. (10638)
89 adher*.tw,kw,kf. (114637)
90 (retain* or retention*).tw,kw,kf. (244370)
91 (non-attend* or nonattend*).tw,kw,kf. (1453)
92 attend*.tw,kw,kf. (110407)
93 (comply* or complies or complian*).tw,kw,kf. (91550)
94 (non-comply* or noncomply* or non-complian* or noncomplian*).tw,kw,kf. (10004)
95 reluctan*.tw,kw,kf. (8504)
96 ((healthcare or care or advice or medical or information) adj3 seek$3).tw,kw,kf. (15252)
97 (disengag* or dis-engag*).tw,kw,kf. (2812)
98 engag*.tw,kw,kf. (82419)
99 avoid*.tw,kw,kf. (237366)
100 ut.fs. (144195)
101 ignor*.tw,kw,kf. (27215)
102 reject*.tw,kw,kf. (82472)

103 (non-embrac* or nonembrac*).tw,kw,kf. (0)
104 (un-embrac* or unembrac*).tw,kw,kf. (1)
105 (embrace* or embracing).tw,kw,kf. (7691)
106 (un-accept* or unaccept*).tw,kw,kf. (14546)
107 (unadher* or un-adher*).tw,kw,kf. (14)
108 no-show*.tw,kw,kf. (484)
109 (follow* adj1 up).tw,kw,kf. (638770)
110 incent*.tw,kw,kf. (17823)
111 enabl*.tw,kw,kf. (214935)
112 disincent*.tw,kw,kf. (859)
113 utiliz*.tw,kw,kf. (319558)
114 (inclin* or disinclin*).tw,kw,kf. (12034)
115 or/72-114 (2984236)

Study type / characteristics

116 randomized controlled trial.pt. (387105)
117 exp Randomized controlled trial/ (387132)
118 exp Randomized Controlled Trials as Topic/ (97414)
119 clinical trial.pt. (490674)
120 Double-Blind Method/ (128228)
121 Placebos/ (32662)
122 clinical trials as topic/ (171490)
123 evaluation research/ (119973)
124 program evaluation/ (47548)
125 Feasibility Studies/ (45412)
126 Pilot Projects/ (85700)
127 Evaluation Studies as Topic/ (119973)
128 Cost-Benefit Analysis/ (61646)
129 (random* or non-random* or unrandom* or nonrandom*).mp,kw,kf. (874470)
130 placebo*.mp,kw,kf. (168179)
131 rct*1.tw,kw,kf. (17367)
132 ((singl* or doubl* or trebl* or tripl*) adj1 (mask* or blind* or dumm*)).mp,kw,kf. (176744)
133 evaluat*.mp,kw,kf. (2416275)
134 effectiv*.mp,kw,kf. (1149619)
135 sustainab*.mp,kw,kf. (23041)
136 feasib*.mp,kw,kf. (177882)
137 appropriateness.mp,kw,kf. (12458)

138 efficac*.mp,kw,kf. (507876)

139 impact*.mp,kw,kf. (537916)

140 (pilot adj2 (project* or study or studies)).mp,kw,kf. (103303)

141 cost-effectiv*.mp,kw,kf. (73309)

142 (cost*1 adj2 benefit*1).mp,kw,kf. (69472)

143 (interrupt* adj2 time).mp,kw,kf. (1224)

144 or/116-143 (4705604)

Lower middle income countries

145 Developing Countries/ (63034)

146 (lmic or lmics or lami countr*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)

147 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)

148 (Afghan* or Albania* or Algeria* or Angola* or Antigua* or Barbud* or Argentin* or Armenia* or Aruba* or Azerbaijan* or Bahrain* or Bangladesh* or Barbad* or Benin* or Byelarus* or Byelorus* or Belarus* or Belorus* or Beliz* or Bhutan* or Bolivia* or Bosnia* or Herzegovin* or Hercegovin* or Botswan* or Brasil* or Brazil* or Bulgaria* or Burkina Faso* or Burkina Fasso* or Upper Volta* or Burundi* or Urundi* or Cambodia* or Khmer Republic or Kampuchea* or Cameroon* or Cameron* or Cape Verde* or Central African Republic or Chad* or Chile* or China or chinese or Colombia* or Comoros* or Comoro Islands or Comores or Mayott* or Congo* or Zair* or Costa Rica* or Cote d'Ivoire or Ivory Coast or Croatia* or Cuba* or Cyprus or cyprian or Czechoslovakia* or Czech Republic or Slovakia* or Slovak Republic or Djibouti* or French Somaliland or Dominica* or East Timor or East Timur or Timor Leste or Ecuador* or Egypt* or United Arab Republic or El Salvador* or Eritrea* or Estonia* or Ethiopia* or Fiji* or Gabon* or Gambia* or Gaza* or Georgia Republic or Georgian Republic or georgian or Ghana* or Gold Coast or Greece or greek or Grenada* or Guatemala* or Guinea* or Guam* or Guiana* or Guyana* or Haiti* or Hondura* or Hungar* or India* or Maldiv* or Indonesia* or Iran* or Iraq* or Isle of Man or Jamaica* or Jordan* or Kazakh* or Kenya* or Kiribati* or Korea* or Kosovo* or Kyrgyz* or Kirghiz* or Kirgiz* or Lao PDR or Laos* or Latvia* or Leban* or Lesotho* or Basutoland or Liberia* or Libya* or Lithuania* or Macedonia* or Madagascar* or Malagasy Republic or Malay* or Sabah* or Sarawak* or Malawi* or Nyasaland* or Mali* or Malta* or Marshall Island* or Maurit* or Agalega Island* or Mexic* or Micronesia* or Middle East* or Moldova* or Moldovia* or Mongolia* or Montenegr* or Morocc* or Ifni* or Mozambiq* or Myanmar* or Myanma or Burma* or Namibia* or Nepal* or Netherlands Antill* or New Caledonia* or Nicaragua* or Niger* or Northern Mariana Island* or Oman* or Muscat* or Pakistan* or Palau* or Palestin* or Panama* or Paragua* or Peru* or Phi?lippin* or Poland or polish or Portug* or Puerto Ric* or Romania* or Rumania* or

Roumania* or Russia* or Rwanda* or Ruanda* or Saint Kitts* or St Kitts or Nevis* or Saint Lucia* or St Lucia* or Saint Vincent* or St Vincent* or Grenadin* or Samoa* or Navigator Island* or Sao Tome* or Saudi Arabia* or saudi or Senegal* or Serbia* or Montenegr* or Seychelles or Sierra Leone or Slovenia* or Sri Lanka* or Ceylon* or Solomon Islands or Somalia* or South Africa* or Sudan* or Surinam* or Swaziland or swazi or Syria* or Tajik* or Tadjik* or Tadzhik* or Tanzania* or Thailand or thai or Togo or Togolese Republic or Tonga* or Trinidad* or Tobag* or Tunisia* or Turkey or turkish or Turkmenistan* or Turkmen* or Uganda* or Ukrain* or Urugua* or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbek* or Vanuat* or New Hebrides or Venezuela* or Vietnam* or Viet Nam* or West Bank or Yemen* or Yugoslavia* or Zambia* or Zimbabw* or Rhodesia* or cabo verd*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)

149 or/145-148 (4677916)

Full topic

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

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

Full topic minus animal-only studies

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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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 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 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 Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 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
DISCUSSION			
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
FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS
Keywords:	HIV, prevention of mother to child transmission, interventions, uptake, retention

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

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Word Count: (4098)

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:

The evidence on effectiveness of interventions to improve uptake and retention of mothers and infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal care may improve ART use during pregnancy. Future studies to replicate promising approaches are needed. Improved reporting of key methodological criteria will facilitate interpretation of findings and improve the utility of evidence to PMTCT program planners.

Systematic review registration: PROSPERO-CRD42015020829

Key Words: HIV, prevention of mother to child transmission, interventions, retention, uptake

Strengths and Limitations of this review:

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

Introduction:

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

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

of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of included studies reported PMTCT outcomes, this was not a primary focus of the review. A second review focused on postpartum retention of women in PMTCT and ART care (14). This review focused on a limited portion of the PMTCT cascade. A third review (15) focused on interventions to improve PMTCT service delivery and promote retention. This review included a range of study designs and studies conducted in both high and low-middle income countries and as such, is of less value as a guide to decision making for PMTCT policy and programming in LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by: lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high income country studies where the context of PMTCT care is often substantially different than in LMICs.

This review was developed in collaboration with knowledge users from the Malawi Ministry of Health's HIV treatment and care technical working group. The objective of this current review was to identify what interventions at the patient, provider, or health system level are effective compared to no intervention or usual care in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health services in LMICs, this review is targeted to provide guidance for PMTCT policy and programming in LMICs, and therefore included a broad range of intervention categories, as well as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.

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). 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

results could be abstracted. No restriction was placed based on language of publication, publication status, study time frame, or duration of follow-up.

Information Sources and Literature Search:

A search strategy was developed in consultation with an experienced information specialist (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review of Electronic Search Strategies checklist (22). The following databases were searched from inception to July 31, 2015 and subsequently updated using the same search strategy for the period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV, pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science, Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE, ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library, WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov. Several databases planned for inclusion in our search were no longer available or not accessible by our group at the time of the search and were therefore not included: AIDS Education Global Information System, British Library Catalogue, and the New York Academy of Grey Literature. In addition, we searched reference lists of included articles, and contacted several experts in the field to inquire about eligible unpublished or in progress studies. See supplementary file for complete MEDLINE search strategy.

Study Selection and Data Collection Process:

A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement. Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then abstracts were screened, and second, the full-text articles were screened. Translation software was utilized to screen articles at the titles and abstracts level, with no non-English articles remaining at the full article review phase. A data abstraction form was created using the EPOC data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in screening and data extraction. A calibration exercise was conducted with completed data extraction forms compared and discussed for each of the first 3 articles to ensure consistency; data extraction was then completed for the remaining articles independently and in duplicate by 2 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each study included: population, intervention, comparator, context, outcomes, study design, time frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment, percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis, and percentage of women and infants retained in PMTCT care/completing the ART regimen as defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants completing post-exposure HIV testing 6 weeks following termination of breast feeding for all infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV; adverse events; major or minor congenital malformations; small for gestational age; pre-mature delivery; still birth; and infant death within first 2 years of life (18).

When necessary to clarify published data or to obtain unpublished data, we contacted primary authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions, and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to calculate risk ratios were not available in the publication. Three responded and provided the requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional data as they were submitting the manuscript for publication.

Methodological Quality/Risk of Bias Appraisal:

Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies included in the meta-analysis, risk of publication bias could not be examined using funnel plots. Selective reporting bias was assessed through review of trial registrations where available and categorized as unclear if not registered.

Data Synthesis:

Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy for health system interventions and discrepancies resolved through discussion (23). Clinical heterogeneity was determined based on patient, intervention, and outcome characteristics. Descriptive synthesis of study results were conducted for all studies, and are reported narratively and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate intervention effects using the Metafor Package in the statistical software R (24). Statistical heterogeneity was examined using the I^2 statistic, with $I^2 \geq 75\%$ indicating significant heterogeneity (16).

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).

Study Characteristics:

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

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 ≥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 • Maternal age (mean): I = 29.3, C = 29.7	1) ART during pregnancy 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 ≥18 and at least 32 weeks gestation	PMTCT providers trained to prepare and counsel women on how to store and	Usual care	• Self-management • 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 478 couples	• % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive • Maternal age (mean): I = 28.3; C = 28.1	1) ART detected in mother blood samples at birth 2) ART detected in infants blood at birth 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 2) Uptake of PMTCT services through to 6 weeks postpartum 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 • Education	8 Clusters 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) 2) ART during labor (AZT or HAART 3) NVP or HAART during labor 4) Infant NVP at birth 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 2444 Patients	% HIV positive at enrollment: 33% overall	NVP in cord blood
Dryden-Peterson; 2015	Provider/System	Stepwedge 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 • Educational meetings	19 Clusters 336 women	% HIV positive: I = 189 (47.6%) and C= 177 (44.6%) • Maternal age (median): (I = 28; C = 29	ART initiation by 30 wks gestation

Mwapasa; 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 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 • The use of information and communication technology	30 Clusters 1350 women	• Maternal age (median): MIP = 29.5; MIP+SMS = 29.2; SOC = 29.4	1) Maternal retention in care at 12 months postpartum trial data 2) Infant retention in care at 12 months postpartum trial data 3) Maternal retention in care at 12 months using MOH definition 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	• Continuous quality improvement	32 Clusters: (6 later excluded) 532 women (21 withdrew leaving 511 in total)	• Maternal age (median): I = 27 ; C = 27	1) ART initiated within 2 week of enrolment 2) Retention in care at 6 months 3) Infants starting prophylaxis within 72 hours 4) infant HIV testing at 6-10 weeks
Phiri; 2017	Provider/System	3 Arm, Cluster RCT	Malawi (SE, SW and Central West	Pregnant and breastfee	FBPS - women received SOC and met with	SOC = standard of care facilities provided	• Role expansion or task shifting outreach	21 Clusters 1269 women	• Maternal age (median across all 3	1) ART uptake 2) Retained 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 • The use of information and communication technology		arms): 27	care at 1 year: 3) Retained in care at 2 years trial data 4) Retained in care at 2 years MOH definition 5) Infant HIV tested at 6 weeks 6) Infant HIV-positive at 6 weeks

					within 1 week of a missed clinic visit.					
Tomlinson; 2014	Provider/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 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.	• Role expansion or task shifting • Outreach services	30 Clusters 3957 women	Maternal age (median): I = 23; C = 23	1) Infant HIV testing by 6 weeks 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 HIV status but had never received treatment	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 partner) participation, and community involvement (male community peer champions providing	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.	• Role expansion/ task shifting Integration • Packages of care	12 Clusters 369 patients	• Maternal age (median): I = 26 ; C = 28	1) Maternal ART initiation 2) Maternal-infant retention in care at 6 week postpartum 3) Maternal-infant retention in care at 12 weeks post 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	• Integration • Educational meetings	6 Clusters	Not available	1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 3) Infant HIV-positive
Killam; 2010	System	Stepwedge 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	• Integration	8 Clusters 31536 patients	• % HIV positive: I = 21.8%; C = 22.2% • Maternal age (mean): I = 27.5; C = 27.3	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	• The use of information and communication technology	388 Patients	• % HIV positive: 29.3% (388/1324) • 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+)	1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks
Rotheram-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	• Role expansion or task shifting • Outreach services	26 Clusters: (2 later removed); 1144 eligible women	• %HIV positive: I = 149 (25.5%); C =146 (26.7%) • Mean maternal age : I = 26.5; C = 26.3	1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART

										at onset of labor 4) Infant prophyl axis within 24 hours of birth 5) AZT dispens ed for infant and medicat ed as prescrib ed 6) Infant HIV test at 6 weeks
Rustagi ; 2016	System	Cluste r RCT	Cote d'Ivoire, Kenya, Mozambi que	Public and non-profit health facilities with PMTCT services. Pregnant women presentin g for antenatal care	A five-step, facility-level systems analysis and improveme nt interventio n designed to maximize effectiveness of PMTCT service delivery by improving understand ing of inefficienci es	Usual care	• Continuou s quality improvem ent	36 Clusters 1876 patients	Not available	1) ART in pregnan cy 2) Infants HIV tested by 6-8 weeks
Turan; 2015	System	Cluste r 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-integrate d ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women to a separate HIV clinic at the same facility	• Integration	12 Clusters: 1172 women	• %HIV positive: I = 48.5%, C = 51.5% • Maternal age (mean): I = 25.0, C = 24.8	1) ART during pregnan cy 2) ART during Labor 3) ART after birth 4) Infant ART after 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

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

Reporting of population characteristics varied widely across studies as did outcome definitions. Seven studies limited participation to pregnant women 17-18 years of age or older; median ages

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

Reported outcomes varied substantially across studies, with few studies within intervention categories reporting comparable outcomes. For example, 5 studies reported interventions employing integration alone [2] or in combination with other interventions [3], with only 1 PMTCT outcome in common among the 2 studies employing integration alone. The most commonly reported outcomes were maternal ART use during pregnancy and labor and delivery, infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.

As a result of the multifaceted nature of the majority of interventions employed, and variability in PMTCT outcomes reported, the ability to combine results statistically was limited.

Methodological Quality:

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

of participants/personnel (18/18) and blinding of outcome assessment (16/18) (The complete risk of bias table is included as an additional file).

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

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

Descriptive Synthesis:

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

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	• Self-management • 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%) 2) ART detected in infants blood at birth: 12/13 (92%) 3) Infant HIV positive at 6 weeks:1/30 (3.3%)	1) ART detected in mother blood samples at birth: I6/12 (50%) 2) ART detected in infants blood at birth: 9/12 (75%) 3) Infant HIV positive: 3/39 (7.7%)	1) 1.50 (0.78-2.88) 2) 1.23 (0.86-1.77) 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%) 2) Uptake of PMTCT services through to 6 wks postpartum:146/216 (67.6%) 3) HIV positive infants at 6 weeks: 5/169 (3.0%)	1) Retention in care at 6 weeks postpartum: 157/217 (72.4%) 2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%) 3) HIV positive infants at 6 weeks: 6/156 (3.9%)	1) 1.11(1.00-1.23) 2) 1.26(1.08-1.48) 3) 0.77(0.24-2.47)	1) ARD 1.13 (1.02-1.26) 2) ARD 1.31 (1.12-1.54) 3) –
Richter, 2014	Patient/Provider	• Role expansion or task shifting • Educational meetings	Peer Mentor led educational meetings	Usual Care	1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%) 2) ART during labor (AZT or HAART): 282/377 (74.8%); 3) NVP or HAART during labor: 361/377 (95.8%) 4) Infant NVP at birth: 364/377 (96.6%) 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%) 2) ART during labor (AZT or HAART): 334/466 (71.7%) 3) NVP or HAART during labor: 456/466 (97.9%) 4) Infant NVP at birth: 451/466 (96.8%) 5) AZT dispensed for infant and medicated as prescribed: 374/466	1) 0.92 (0.89-0.96) 2) 1.04 (0.96-1.13) 3) 0.98 (0.95-1.00) 4) 1.00 (0.97-1.02) 5) 1.15 (1.09-1.21)	1) AOR 0.44 (0.26,0.74) 2) AOR 1.16(0.44, 3.02) 3) AOR 0.53 (0.20, 1.41) 4) AOR 1.00 (0.36, 2.79) 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-Peterson; 2015	Provider/System	• The use of information and communication technology	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					
Mwapasa; 2017	Provider/System	• Integration • The use of information and communication technology	MIP= integration of antenatal and HIV care, routine patient tracing 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% MIP+SMS 115/493 2) Infant retention in care at 12 months postpartum trial data: MIP 32/386, 8.3% MIP+SMS 82/399, 20.1% 3) Maternal retention in care at 12 months using MOH definition: MIP 334/461, 72.4% MIP+SMS 332/493, 67%. 4) Infant retention in care at 12 months using MOH definition: MIP 291/386, 75.4% MIP+SMS 323/399, 80.9%	1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396, 22.7% 2) Infant retention in care at 12 months postpartum trial data: SOC 32/300,10.7 3) Maternal retention in care at 12 months using MOH definition: SOC 274/396, 69.1% 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) 2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82) 3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06) 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) 2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31) 3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05) 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/System	• Continuous quality improvement	QI teams established, coaching, and collaborative meetings	Routine MOH support	1) ART initiated within 2 week of enrolment: 261/264 = 98.9% 2) Retention in care at 6 months. 117/264 = 44.3% 3) Infants starting prophylaxis within 72 hours : 138/209 = 66**%** 4) Infant HIV testing at 6-10 weeks 102/209 = 48.8%;	1) ART initiated within 2 week of enrolment: 233/247 = 94.3% 2) Retention in care at 6 months. 102/247 = 41.3% 3) Infants starting prophylaxis within 72 hours 145/194 = 74.7% 4) Infant HIV testing at 6-10 weeks: 49/194 = 25.3%	1) 1.05 (1.01-1.08) 2) 1.07 (0.88-1.31) 3) 0.88 (0.78-1.00) 4) 1.93 (1.46-2.55)	1) -- 2) ARR 1.08(0.78, 1.49) 3) ARR 0.95 (0.84, 1.07) 4) ARR 1.76(1.27, 2.42)
Phiri; 2017	Provider/System	• Role expansion or task shifting outreach services • The use of information and communication technology	FBPS – facility based peer support from mentor mothers CBPS- community based peer support from	SOC- standard of care	1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%) 2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%) 3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394	1) ART uptake: SOC- 361/447(81%) 2) Retained in care at 1 year: SOC- 261/361 (74%) 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) 2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10) 3) SOC vs FBPS 1.38(1.19-	1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18) 2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20) 3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30) 4) --

			mentor mothers		(54%) 4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%) 5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%) 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%) 5) Infant HIV test at 6 weeks: SOC- 169/273(62%) 6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)	1.60), SOC vs CBPS 1.42 (1.22-1.65) 4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43) 5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38) 6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09)	5) -- 6) ---
Tomlinson: 2014	Provider/System	• Role expansion or task shifting • Outreach services	10 structured home visits from community health workers addressing PMTCT and newborn care	3 home visits from community health workers providing support in accessing social welfare grants	1) Infant HIV testing by 6 weeks: 420/571(73.6%) 2) Infant HIV positive at 12 weeks: 28/568 (4.9%)	1) Infant HIV testing by 6 weeks: 465/698(66.6%) 2) Infant HIV positive at 12 weeks: 32/697 (4.6%)	1) 1.10 (1.03-1.19) 2) 1.07 (0.65-1.76)	1) ARR 1.10 (0.97, 1.25) 2) ARR 1.07 (0.69,1.66)
Aliyu; 2016	System	• Role expansion /task shifting Integration • Packages of care	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%) 3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)	1) Maternal ART initiation for PMTCT: 77/197 (39%), 2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%) 3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%)	1) 2.47 (2.07-2.95) 2) 9.44 (5.60-15.40) 3) 11.40 (6.40-20.34)	1) ARR 3.3 (1.4-7.8) 2) ARR 9.1 (5.2-15.9) 3) ARR 10.3(5.4-19.7)
Geelhoed; 2013	System	• Integration • Educational meetings	Integrated maternal child health and HIV care	Usual Non-integrated care	1) ART in labor: post intervention:112/121 (93%) 2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%); 3) Infants HIV-positive: post intervention: 9/123 (7%)	1) ART in labor: intervention phase =93/96(97%) 2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%) 3) Infants HIV positive: intervention phase: 7/60(12%)	1) 0.96 (0.90-1.02) 2) 0.93 (0.88-0.97) 3) 0.63 (0.25-1.60)	-- -- --
Killam; 2010	System	• Integration	Integration of antenatal	Usual non-integrat	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%) 2) Infant HIV testing by 8 wks: I172/187 (92.0%)	1) Maternal postpartum clinic attendance: 22/187 (11.8%) 2) Infant HIV testing by 8 wks: 154/181 (85.1%)	1) 1.66 (1.03-2.70) 2) 1.08 (1.00-1.16)	-- -
Rotheram-Borus; 2014	System	• Role expansion or task shifting • Outreach services	Antenatal and postnatal home visits from community health workers	Usual care	1) ART prior to labor: 169/179 (94.4%) 2) AZT or HAART during labor: I164/179 (91.6%) 3) NVP or HAART at onset of labor: 166/179 (92.7%) 4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%) 5) Infant ART after birth: 172/179 (96.1%) 6) Infant HIV testing at 6 weeks: 155/160 (96.9%)	1) ART prior to labor: 149/159 (93.7%) 2) AZT or HAART during labor: 147/159 (92.5%) 3) NVP or HAART at onset of labor: 142/159 (89.3%) 4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%) 5) Infant ART after birth: 142/159 (89.3%) 6) Infant HIV testing at 6 weeks: 132/140 (94.3%)	1) 1.01 (0.95-1.06) 2) 0.99 (0.93-1.06) 3) 1.04 (0.97-1.11) 4) 1.08 (1.01-1.15) 5) 1.08 (1.01-1.14) 6) 1.03 (0.98-1.08)	1) AOR 1.08 (0.42, 2.80) 2) AOR 0.87 (0.39, 1.95) 3) AOR 1.52(0.70, 3.31) 4) AOR 2.94(1.41, 6.12) 5) AOR 2.95 (1.12, 7.73) 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%) 2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)	1) ART in pregnancy: 664/1037(64%) 2) Infant HIV tested by 6-8 wks: C = 270/710.6 (38%)	1) 1.07 (1.00-1.14) 2) 1.23 (1.09-1.40)	-- --
Turan; 2015	System	• Integration	Integrated HIV and antenatal care	Usual, non-integrated care	1) ART during pregnancy: 138/173 (80%) 2) ART during Labor: 28/173 (16%) 3) ART after birth: 22/173 (13%) 4) Infant ART after birth: 50/173 (29%) 5) ART throughout all 3 PMTCT periods: 37/176 (21.0%) 6) Infant HIV testing before 3 months: 143/569 (25%) 7) Infant HIV testing at 9 months: 361/569 (63%) 8) Infants HIV tested by 6 weeks: 143/568 (25%) 9) Infants HIV positive at 6	1) ART during pregnancy: 75/152 (49%) 2) ART during Labor: 84/152 (55%) 3) ART after birth: 57/152 (38%) 4) Infant ART after birth: 106/152 (70%) 5) ART throughout all 3 PMTCT periods: 23/153 (15.0%) 6) Infant HIV testing before 3 months: 106/603 (18%) 7) Infant HIV testing at 9 months: 326/603 (54%) 8) Infants HIV tested by 6 weeks: 106/594 (18%) 9) Infants HIV positive at 6	1) 1.61 (1.35-1.93) 2) 0.29 (0.20-0.42) 3) 0.34 (0.22-0.53) 4) 0.41 (0.32-0.54) 5) 1.40 (0.87-2.24) 6) 1.43 (1.14-1.79) 7) 1.17 (1.07-1.29) 8) 1.41 (1.13-1.76) 9) 0.64 (0.22-1.84)	1) AOR 4.05 (2.0, 8.0) 2) AOR 0.16 (0.04, 0.68) 3) AOR 0.24 (0.08, 0.70) 4) AOR 0.18 (0.09, 0.35) 5) AOR 1.72 (0.85, 3.48) 6) AOR 1.57 (0.61,4.07) 7) AOR 1.47 (0.76,2.86) 8) AOR 1.57 (0.61-4.07) 9) AOR 0.62 (0.20,1.98) 10) AOR 1.45 (0.71,2.82)

					weeks: I6/143 (4.2%) 10) Infants HIV tested by end of study (up to 12 m): 382/568 (67.3%) 11) Infants HIV positive at 9 months: 28/382 (7.3%)	weeks: 7/106 (6.6%) 10) Infants HIV tested by end of study (up to 12 m): 338/594 (57.0%) 11) Infants HIV positive at 9 months: 27/338 (8.0%)	10) 1.18 (1.08-1.29) 11) 0.92 (0.55-1.53)	11) AOR 0.89 (0.56,1.43)

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

Synthesis of findings according to intervention type and target:

Patient Level Interventions:

Four studies evaluated interventions primarily targeted at the patient level (27,28,29,30). Risk of bias ranged from 3 to 6 of 6 criteria rated as high or unclear. Ezeanolue et al. (27) included 40 clusters and 3,024 patients and evaluated a complex intervention that included monthly baby showers at participating churches where expectant mothers participated in educational games, received 'mama packs' containing supplies needed during delivery (sterile gloves, alcohol swabs, clean razor, etc.) and laboratory testing, and were given a contact point for follow-up. Women in the intervention group were found to be significantly more likely to complete linkage to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided

pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT intervention compared to standard care. They found no statistically significant difference in PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and evaluated whether conditional cash transfers improved adherence, acceptance of and retention in PMTCT services to 6 weeks postpartum. They found women in the intervention group were significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95% CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.

Patient/Provider Level Interventions:

One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention directed at both patients and providers in which peer mentors were trained to provide in person education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31). They found patients in the intervention group were significantly less likely to adhere to ARTs during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-0.74]). No statistically significant effects were found on the remaining outcomes including: ART use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were unable to reach authors for additional information on long term outcomes.

Provider Level Interventions:

Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day PMTCT knowledge and skills training course for nurses and midwives compared to standard training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They found a statistically significant increase in the proportion of women with ART detected in cord blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).

Provider/System Level Interventions:

Five studies reported interventions directed at both the provider and health system level (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated transmission of HIV test results to clinic staff via short message service (SMS), and ongoing support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring and addressing clinic underperformance). There was a trend towards an increase in the proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.

Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing (MIP+SMS) combined with integrated care against standard care (SOC). They found no significant difference in maternal retention in care at 12 months in either intervention group relative to controls using study definitions, or ministry of health definitions for retention. They found no statistically significant difference in infant retention in care at 12 months in either

intervention group relative to controls using study definitions, or ministry of health definitions for retention .

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

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

Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased training of community health workers and increased home visits by community health workers during and post delivery to provide PMTCT counselling and newborn care. They found a significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in mother to child HIV transmission at 12 weeks.

System Level Interventions:

Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community involvement through male champions, compared to standard care across 12 clusters and 369 patients. They found significant improvement in the proportion of eligible women 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 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-19.7]).

Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and evaluated the impact of integration of HIV and maternal child health services during both antenatal and postnatal periods. They found no improvement in the proportion of women

receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48 hours and the proportion of HIV positive infants.

Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a statistically significant increase in the proportion of eligible women receiving ARTs during pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).

Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during pregnancy and post-delivery. They found statistically significant improvements in maternal antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks (RR= 1.08 [1.00-1.16]).

Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.

Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters in 3 countries, including 1876 patients. They found no significant improvement in the proportion

of pregnant women receiving ARTs (RR= 1.07 [95% CI 1.00- 1.14]) or infants tested for HIV by 6-8 weeks (RR= 1.23 [95% CI 1.09-1.40]).

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

Synthesis of findings according to PMTCT outcomes:

The vast majority of studies reported short-term PMTCT outcomes with ART use during pregnancy (10/18) and labor and delivery (6/18), infant prophylaxis at birth (6/18), and infant HIV testing at 6-10 weeks (5/18). Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance.

Five studies found significant improvements in ART use during pregnancy ranging with RR ranging from 1.12 to 2.48 (25, 26, 27, 36, 38). Effective interventions included: integration of

ANC and HIV services (RR= 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]) (25) and (RR= 2.28 [95% CI 1.86-2.80] AOR= 2.01 [95% CI 1.37-2.95]) (26); monthly baby showers at participating churches providing education through games, 'mama packs' containing delivery supplies, laboratory testing, and a contact point for follow-up (RR 1.56 [95% CI 0.93-2.62], AOR=2.8 [95% CI 1.02-4.79]) (27); community based peer support from mentor mothers (RR= 1.12 [95% CI 1.06-1.18], ARD 0.09 [95% CI 0.01-0.18]) (36) ; and an integrated package of PMTCT services including point-of-care CD4 testing, decentralized PMTCT care, integrated mother/infant services, and community champions, (RR= 2.47 [95% CI 2.07-2.95], ARR 3.3 [95% CI 1.4-7.8]) (38). Four studies evaluating: staff training and support to ante-natal clinics, and automated SMS transmission of HIV test results to clinic staff (33); a quality improvement initiative (35); community health worker ante- and post-natal home visits (41); and facility level systems analysis and improvement intervention (42), found no significant difference in ART use during pregnancy. One study evaluating peer mentor led educational meetings, found ART adherence during pregnancy lower in the intervention group (31).

Six studies reported ART use during labor and delivery, with 4/6 finding no significant effect (29, 31, 39, 41)), 1 finding a significant but small improvement RR=1.17 (32) and 1 finding significantly reduced ART use in the intervention group RR=1.614 (25). The one study that found a small significant effect employed a 1-day PMTCT knowledge and skills training course for nurses and midwives (RR= 1.17 [95% CI 1.08-1.26]) (32). Ineffective interventions included; couples based PMTCT intervention (29), peer mentor led educational meetings (31), integration of maternal child health and HIV services (39), and community health worker ante-natal and post-partum home visits (41). In contrast to the findings for ART use during pregnancy, ART

use during labor and delivery was low significantly lower with integration of ANC and HIV care (25) RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI 0.04, 0.68] (25).

Only 1 study evaluated ART use in the post-partum period and found significantly reduced ART use during this period (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]) with integration of ANC and HIV care (25).Two additional studies evaluated uptake across the cascade, with conditional cash transfer found to significantly improve uptake of PMTCT recommendations (RR= 1.26 [95% CI 1.08-1.48]) (30) and no difference found for integration of ANC and HIV services (25).

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

Seven studies reported infant HIV testing at 6 weeks. Three of 7 found significantly improved rates of infant testing by 6-10 weeks of age with RR ranging from 1.08 to 1.93 (35,37,40), 3/7 no difference (25, 41,42), and one study finding a mixed effect of peer support (36). Improvements in infant HIV testing were found for a quality improvement intervention

(RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-2.42]) (35), increased training of and home visits from community health workers (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) (37), and SMS texts to patients both antenatally and post-delivery (RR= 1.08 [1.00-1.16]) (40). One study found mixed effects of peer support on infant HIV testing, with community based peer support found to significantly improve infant HIV testing at 6 weeks (RR=1.23 [95% CI 1.11-1.38]) and no difference found for facility based peer support (36). No difference was found for integration of ANC and HIV care (25), home visits from community health workers (41) or a facility level analysis and quality improvement intervention (42).

Outcome definitions for retention in care and infant HIV-positive rates were highly variable, ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant retention in care at 6 weeks, with 2 studies evaluating conditional cash transfers (30) and an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community champions (38), finding significantly improved retention (RR= 1.11 [95% CI 1.00-1.23]) and at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) (38), and a third employing monthly baby showers finding no difference (27).

Four studies examined infant HIV-positive rates at 6 weeks post-partum. Evaluated interventions included; integration of ANC and HIV care (25), couples based HIV/PMTCT counselling (29), conditional cash transfers (30), and peer support (36). All found no difference.

Discussion:

Eighteen studies were included in our review. Heterogeneity of interventions and outcome reported limited both comparison across studies and intervention categories, as well as, opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias, primarily due to limitations inherent to health systems research and unclear reporting of key methodological factors.

Based on our review findings, several interventions appear promising. In the single meta-analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use during pregnancy with integration of HIV and antenatal care compared to standard non-integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies found small positive effects of integration of HIV and antenatal care, alone or as part of a complex intervention, on ART use during pregnancy. However, the effects of integration on PMTCT outcomes during labor and delivery, and post-delivery were less clear, with no difference found for some studies (39, 34) and for some outcomes (25), and one study finding reduced ART use during labor and delivery, and post-delivery (25).Therefore, as integrated care is increasingly common future work focusing on how integration of maternal child health and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes beyond the antenatal period is needed.

Four studies evaluating different approaches to outreach services alone or in combination with other interventions found small positive effects on linkage to care, ART use during pregnancy

and labor/delivery, and early infant HIV testing. Two studies found positive effects of role expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy and, when combined with outreach services, positive effects were seen on long term retention in care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT outcomes, each in a single study, included: educational meetings, conditional cash transfers, continuous quality improvement, and use of information and communication technology.

An important finding of the present review is the high degree of variability in outcome definitions and relative lack of longer-term outcome data. While in some instances variability of outcome definitions may be considered a strength where both self-report and biological markers of ART use are included, variability in timing of outcomes limits comparison across studies and opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is clearly critical to reducing HIV transmission, longer term outcomes are equally important to understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of future work would be substantially improved through both standardization of timing of PMTCT outcomes and through funding opportunities that would allow for evaluation of longer term outcomes.

In keeping with other systematic reviews focused on interventions aimed at improving PMTCT care and outcomes published to date (8,9,13,14,15), our review found the evidence base available to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor Car et al. (9), which included a single study and found improved ART use in labor/delivery from

integration of care, our single meta-analysis including 2 studies found a positive effect of integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only 2 of which met inclusion criteria for the present review, and they also found variable effects of non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al. (14) included 10 articles, with 2 overlapping studies included in our review, and focused on postpartum retention of women in PMTCT and ART care. This latter review, which included both high and LMICs and a broader range of study designs, focused on a limited portion of the PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to improve PMTCT service delivery and promote retention. Their review was conducted over a similar timeframe to the present review, however, it differs from the present review in its inclusion of high income country studies, inclusion of a range of study designs, and in its approach to categorization of interventions. Thirty-four studies were included in their review, 11 of which were included in the present review. They found weak evidence for improvement of early infant HIV diagnosis from mobile-phone based interventions and for male involvement in reducing infant HIV transmission.

Given the focus of the present review on providing evidence-based guidance to PMTCT program planners and implementers based LMICs our review differs from the reviews noted above in several ways. First, to optimize the quality of evidence we limited our review to randomized and non-randomized controlled trials and interrupted times series studies. Second, to increase the applicability of findings to LMIC implementers, we limited our review to studies conducted in LMICs. Third, we included a broad range of intervention categories and included both maternal

and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to provide information of direct relevance to implementation planning, we categorized and analyzed interventions at both the level at which they are implemented (patient, provider, system) and using the EPOC intervention classification scheme, which groups interventions based on the intervention process/activities employed.

Limitations:

While agreement on data extraction was not calculated, an initial calibration exercise was carried out to ensure consistency in data extraction. Following this, comparison of completed data extraction forms revealed few differences. Although no study was excluded for language, it is possible that use of translation software may have resulted in exclusion of an eligible study due to inaccurate translation. Additionally, while unlikely to have led to a significant difference in results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO as the later was not accessible to the second information technologist.

The multifaceted nature of the majority of interventions evaluated and variability in PMTCT outcomes reported, limited our ability to combine studies statistically and to separate effective/ineffective features of the interventions. In addition, efforts to contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due to the small number of studies included in the meta-analysis publication bias could not be examined. Additionally, although pre-specified in our protocol, interpretation of findings, most commonly infant HIV infection rates, are limited by lack of power to assess secondary outcomes among included

studies. As 7 of the 18 studies limited participation to women 17-18 years of age or older, results may be less generalizable to younger mothers. Finally, although the EPOC search filter is designed to identify articles from all low- and middle-income countries, only articles from Sub-Saharan Africa were included in the review. Results therefore may be less generalizable to LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the evidence to date and where funding should be targeted for future research based on knowledge users needs.

Future Directions:

Overall, evidence to date to guide PMTCT programming is limited. In particular, effects were generally small and often mixed across studies, and based on a small number of studies that were largely at moderate to high risk of bias. Further research is needed both to improve quantity and quality of data. First, replication of promising approaches is needed. Second, improved publication reporting to ensure key methodological factors are addressed and to provide detail on the likely impact of factors that cannot be modified through design. This transparency in reporting will enhance interpretation and utility of findings in informing PMTCT policy and program decision making. For example, while the nature of designs for evaluating PMTCT interventions, often make blinding of participants impossible, description of the context and likely impact would aid interpretation. Additionally, use of blinded outcome assessment or objective outcomes such as laboratory confirmation of ART in blood samples will increase study impact. Third, given the inherent difficulties in evaluating complex interventions, increased use of designs to facilitate evaluation, for example, factorial designs of multiple arm studies, would be of value. Fourth, efforts to include a variety of key outcomes across the PMTCT cascade and

longer term outcomes in particular where feasible, would allow for increased comparison across interventions.

Conclusions:

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

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

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***Authors' contributions*:** LPR and MvL conceived the study. LPR and SS developed the search strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence tables and manuscript. LPR conducted the meta-analysis with support from BP. MCH, NER, SP, ML, and FC provided content expertise and assisted with preparation of the protocol and manuscript. All authors provided critical revision of the manuscript and read and approved the final manuscript.

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Captions for appended Tables and Figures:

Table 1: Characteristics of Included Studies

Table 2: Results of Included Studies

Figure 1: PRISMA diagram of search results and screening

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

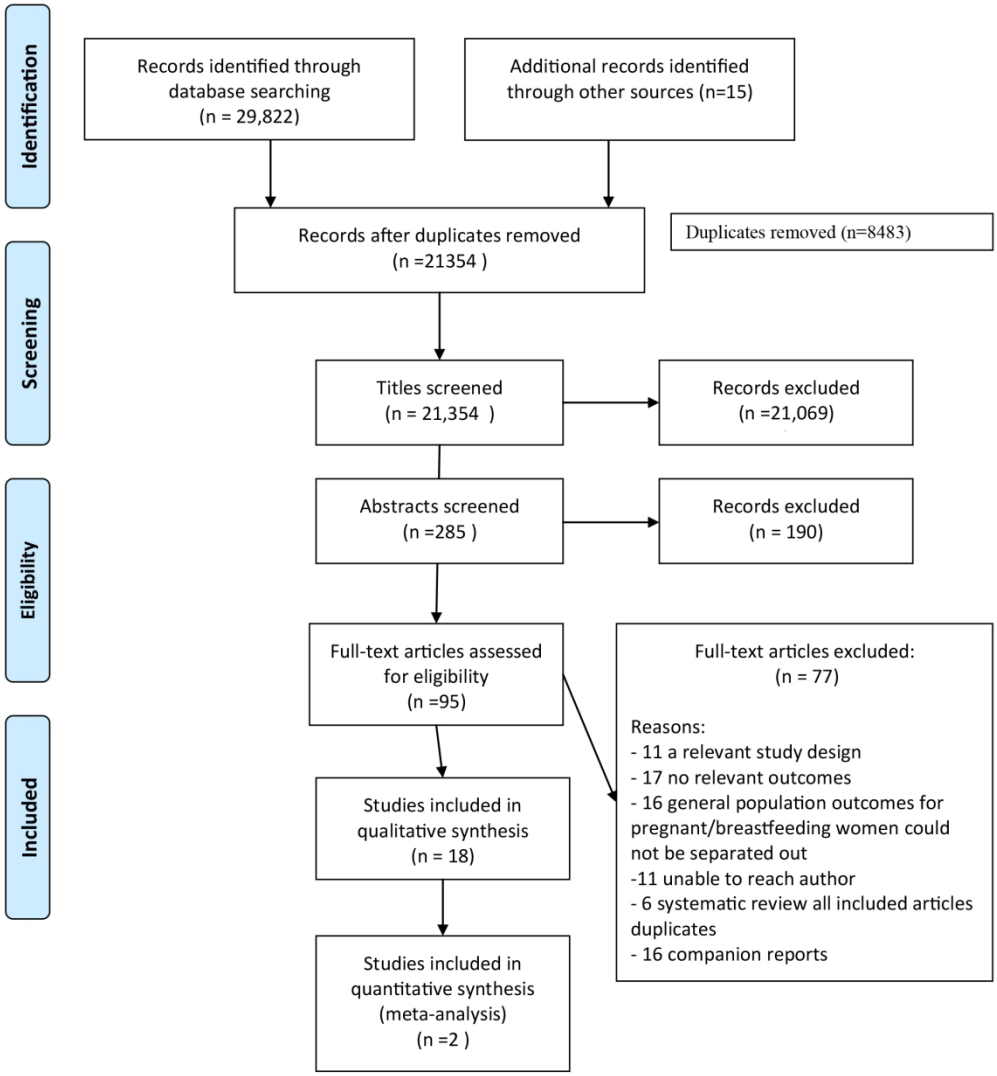


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

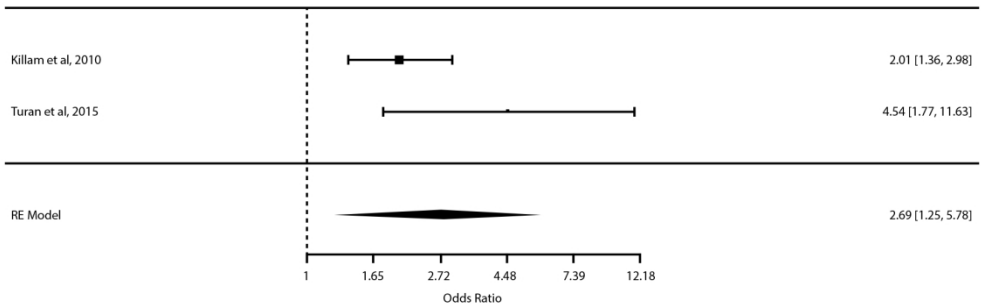
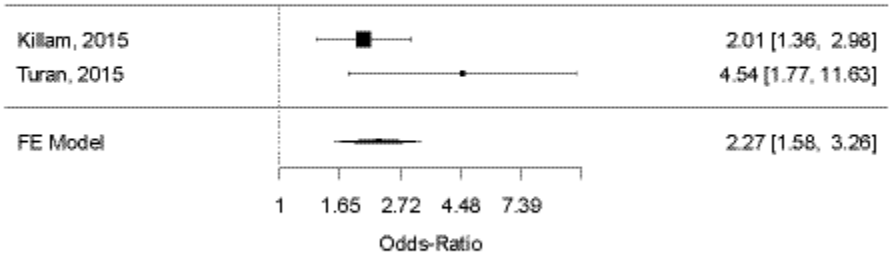


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)


Killam, 2015
Turan, 2015
FE Model
2.01 [1.36, 2.98]
4.54 [1.77, 11.63]
2.27 [1.58, 3.26]
1
1.65
2.72
4.48
7.39
Odds-Ratio

Search Strategy Ovid MEDLINE(R) <1946 to June Week 2 2018>:

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)

34 (breast adj2 fed*).tw,kw,kf. (5276)
35 in-utero.tw,kw,kf. (20490)
36 (intrauterine or intra-uterine).tw,kw,kf. (42420)
37 (trans-placent* or transplacent*).tw,kw,kf. (5212)
38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)
39 (parent* adj2 (child* or infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (28605)
40 mother*.tw,kw,kf. (147803)
41 (nursing adj2 (infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (1319)
42 (prenatal* or pre-natal*).tw,kw,kf. (70920)
43 (perinatal* or peri-natal*).tw,kw,kf. (51747)
44 (post-natal* or postnatal*).tw,kw,kf. (85370)
45 (antenatal* or antenatal*).tw,kw,kf. (23135)
46 (antepartum* or ante-partum*).tw,kw,kf. (4566)
47 (postpartum* or post-partum*).tw,kw,kf. (40829)
48 maternal*.tw,kw,kf. (172644)
49 or/1-48 (1763167)

HIV/AIDS

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)

68 (aids adj1 related).tw,kw,kf. (6614)
69 htlv*.tw,kw,kf. (11427)
70 hiv##.mp,kw,kf. (1760)
71 or/50-70 (325026)

Patient uptake / dropouts / participation
72 Patient Dropouts/ (6786)
73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)
74 exp Consumer Participation/ (32566)
75 dropout*.tw,kw,kf. (6483)
76 (uptake or up-take).tw,kw,kf. (248330)
77 (drop* adj1 out$1).tw,kw,kf. (8228)
78 (refusal* or refuse$1 or refusing).tw,kw,kf. (23366)
79 (patient* adj2 (elope or elope$1 or eloping)).tw,kw,kf. (4)
80 (non complian* or noncomplian*).tw,kw,kf. (9990)
81 complian*.tw,kw,kf. (84306)
82 (uncooperat* or unco-operat* or un-co-operat*).tw,kw,kf. (1028)
83 (cooperat* or co-operat*).tw,kw,kf. (102475)
84 (non-accept* or nonaccept*).tw,kw,kf. (592)
85 accept*.tw,kw,kf. (279089)
86 (nonparticipat* or non-participat*).tw,kw,kf. (1298)
87 participat*.tw,kw,kf. (322007)
88 (nonadher* or non-adher*).tw,kw,kf. (10638)
89 adher*.tw,kw,kf. (114637)
90 (retain* or retention*).tw,kw,kf. (244370)
91 (non-attend* or nonattend*).tw,kw,kf. (1453)
92 attend*.tw,kw,kf. (110407)
93 (comply* or complies or complian*).tw,kw,kf. (91550)
94 (non-comply* or noncomply* or non-complian* or noncomplian*).tw,kw,kf. (10004)
95 reluctan*.tw,kw,kf. (8504)
96 ((healthcare or care or advice or medical or information) adj3 seek$3).tw,kw,kf. (15252)
97 (disengag* or dis-engag*).tw,kw,kf. (2812)
98 engag*.tw,kw,kf. (82419)
99 avoid*.tw,kw,kf. (237366)
100 ut.fs. (144195)
101 ignor*.tw,kw,kf. (27215)
102 reject*.tw,kw,kf. (82472)

103 (non-embrac* or nonembrac*).tw,kw,kf. (0)
104 (un-embrac* or unembrac*).tw,kw,kf. (1)
105 (embrace* or embracing).tw,kw,kf. (7691)
106 (un-accept* or unaccept*).tw,kw,kf. (14546)
107 (unadher* or un-adher*).tw,kw,kf. (14)
108 no-show*.tw,kw,kf. (484)
109 (follow* adj1 up).tw,kw,kf. (638770)
110 incent*.tw,kw,kf. (17823)
111 enabl*.tw,kw,kf. (214935)
112 disincent*.tw,kw,kf. (859)
113 utiliz*.tw,kw,kf. (319558)
114 (inclin* or disinclin*).tw,kw,kf. (12034)
115 or/72-114 (2984236)

Study type / characteristics

116 randomized controlled trial.pt. (387105)
117 exp Randomized controlled trial/ (387132)
118 exp Randomized Controlled Trials as Topic/ (97414)
119 clinical trial.pt. (490674)
120 Double-Blind Method/ (128228)
121 Placebos/ (32662)
122 clinical trials as topic/ (171490)
123 evaluation research/ (119973)
124 program evaluation/ (47548)
125 Feasibility Studies/ (45412)
126 Pilot Projects/ (85700)
127 Evaluation Studies as Topic/ (119973)
128 Cost-Benefit Analysis/ (61646)
129 (random* or non-random* or unrandom* or nonrandom*).mp,kw,kf. (874470)
130 placebo*.mp,kw,kf. (168179)
131 rct*1.tw,kw,kf. (17367)
132 ((singl* or doubl* or trebl* or tripl*) adj1 (mask* or blind* or dumm*)).mp,kw,kf. (176744)
133 evaluat*.mp,kw,kf. (2416275)
134 effectiv*.mp,kw,kf. (1149619)
135 sustainab*.mp,kw,kf. (23041)
136 feasib*.mp,kw,kf. (177882)
137 appropriateness.mp,kw,kf. (12458)

138 efficac*.mp,kw,kf. (507876)

139 impact*.mp,kw,kf. (537916)

140 (pilot adj2 (project* or study or studies)).mp,kw,kf. (103303)

141 cost-effectiv*.mp,kw,kf. (73309)

142 (cost*1 adj2 benefit*1).mp,kw,kf. (69472)

143 (interrupt* adj2 time).mp,kw,kf. (1224)

144 or/116-143 (4705604)

Lower middle income countries

145 Developing Countries/ (63034)

146 (lmic or lmics or lami countr*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)

147 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)

148 (Afghan* or Albania* or Algeria* or Angola* or Antigua* or Barbud* or Argentin* or Armenia* or Aruba* or Azerbaijan* or Bahrain* or Bangladesh* or Barbad* or Benin* or Byelarus* or Byelorus* or Belarus* or Belorus* or Beliz* or Bhutan* or Bolivia* or Bosnia* or Herzegovin* or Hercegovin* or Botswan* or Brasil* or Brazil* or Bulgaria* or Burkina Faso* or Burkina Fasso* or Upper Volta* or Burundi* or Urundi* or Cambodia* or Khmer Republic or Kampuchea* or Cameroon* or Cameron* or Cape Verde* or Central African Republic or Chad* or Chile* or China or chinese or Colombia* or Comoros* or Comoro Islands or Comores or Mayott* or Congo* or Zair* or Costa Rica* or Cote d'Ivoire or Ivory Coast or Croatia* or Cuba* or Cyprus or cyprian or Czechoslovakia* or Czech Republic or Slovakia* or Slovak Republic or Djibouti* or French Somaliland or Dominica* or East Timor or East Timur or Timor Leste or Ecuador* or Egypt* or United Arab Republic or El Salvador* or Eritrea* or Estonia* or Ethiopia* or Fiji* or Gabon* or Gambia* or Gaza* or Georgia Republic or Georgian Republic or georgian or Ghana* or Gold Coast or Greece or greek or Grenada* or Guatemala* or Guinea* or Guam* or Guiana* or Guyana* or Haiti* or Hondura* or Hungar* or India* or Maldiv* or Indonesia* or Iran* or Iraq* or Isle of Man or Jamaica* or Jordan* or Kazakh* or Kenya* or Kiribati* or Korea* or Kosovo* or Kyrgyz* or Kirghiz* or Kirgiz* or Lao PDR or Laos* or Latvia* or Leban* or Lesotho* or Basutoland or Liberia* or Libya* or Lithuania* or Macedonia* or Madagascar* or Malagasy Republic or Malay* or Sabah* or Sarawak* or Malawi* or Nyasaland* or Mali* or Malta* or Marshall Island* or Maurit* or Agalega Island* or Mexic* or Micronesia* or Middle East* or Moldova* or Moldovia* or Mongolia* or Montenegr* or Morocc* or Ifni* or Mozambiq* or Myanmar* or Myanma or Burma* or Namibia* or Nepal* or Netherlands Antill* or New Caledonia* or Nicaragua* or Niger* or Northern Mariana Island* or Oman* or Muscat* or Pakistan* or Palau* or Palestin* or Panama* or Paragua* or Peru* or Phi?lippin* or Poland or polish or Portug* or Puerto Ric* or Romania* or Rumania* or

Roumania* or Russia* or Rwanda* or Ruanda* or Saint Kitts* or St Kitts or Nevis* or Saint Lucia* or St Lucia* or Saint Vincent* or St Vincent* or Grenadin* or Samoa* or Navigator Island* or Sao Tome* or Saudi Arabia* or saudi or Senegal* or Serbia* or Montenegr* or Seychelles or Sierra Leone or Slovenia* or Sri Lanka* or Ceylon* or Solomon Islands or Somalia* or South Africa* or Sudan* or Surinam* or Swaziland or swazi or Syria* or Tajik* or Tadjik* or Tadzhik* or Tanzania* or Thailand or thai or Togo or Togolese Republic or Tonga* or Trinidad* or Tobag* or Tunisia* or Turkey or turkish or Turkmenistan* or Turkmen* or Uganda* or Ukrain* or Urugua* or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbek* or Vanuat* or New Hebrides or Venezuela* or Vietnam* or Viet Nam* or West Bank or Yemen* or Yugoslavia* or Zambia* or Zimbabw* or Rhodesia* or cabo verd*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)

149 or/145-148 (4677916)

Full topic

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

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

Full topic minus animal-only studies

152 150 not 151 (3291)

****

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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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 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 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 Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 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
DISCUSSION			
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
FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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:	*BMJ Open*
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 van Lettow, Monique; Dignitas International; University of Toronto Dalla Lana School of Public Health Pham, Ba; Li Ka Shing Knowledge Institute, St. Michael's Hospital Straus, Sharon; St. Michael's Hospital, Li Ka Shing Knowledge Institute; University of Toronto, Department of Medicine Hosseinipour, Mina C.; University of North Carolina, Division of Infectious Disease; University of North Carolina Project Rosenberg, Nora; University of North Carolina; University of North Carolina Project Phiri, Sam; University of North Carolina, Department of Health Behavior, School of Public Health; Lighthouse Trust Landes, Megan; University Health Network, Department of Emergency Medicine; University of Toronto, Department of Family and Community Medicine Cataldo, Fabian; Dignitas International; University of Toronto, Dalla Lana School of Public Health
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS
Keywords:	HIV, prevention of mother to child transmission, interventions, uptake, retention

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

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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:

The evidence on effectiveness of interventions to improve uptake and retention of mothers and infants in PMTCT care is lacking. Our findings suggest that integration of HIV and antenatal care may improve ART use during pregnancy. Future studies to replicate promising approaches are needed. Improved reporting of key methodological criteria will facilitate interpretation of findings and improve the utility of evidence to PMTCT program planners.

Systematic review registration: PROSPERO-CRD42015020829

Key Words: HIV, prevention of mother to child transmission, interventions, retention, uptake

Strengths and Limitations of this review:

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

Introduction:

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

Eight systematic reviews have been conducted on strategies to optimize PMTCT. Two of these reviews evaluated the effectiveness of interventions, specifically, male involvement (8) and integration of services (9), to improve coverage of PMTCT services. These reviews were limited by the lack of studies to provide recommendations. A third review (10) examined the effects of integration of antenatal care with postnatal and other health services for a broad range of maternal health outcomes in LMICs; although some PMTCT studies and outcomes were included, this was not the focus of the review. A fourth systematic review evaluated interventions for improving initiation of antiretroviral therapy (ART) therapy in pregnant women (11) and found the evidence quality insufficient to support recommendations. A fifth systematic review (12) assessed the impact of China's PMTCT cascade in improving uptake and outcomes at various steps along the cascade; specific interventions implemented to operationalize the cascade were not reported. Three systematic reviews have been published since the initiation of the present review. One review evaluated non-pharmacological interventions to improve quality of care and maternal health outcomes in Sub-Saharan Africa (13). While a small number of

included studies reported PMTCT outcomes, this was not a primary focus of the review. A second review focused on postpartum retention of women in PMTCT and ART care (14). This review focused on a limited portion of the PMTCT cascade. A third review (15) focused on interventions to improve PMTCT service delivery and promote retention. This review included a range of study designs and studies conducted in both high and low-middle income countries and as such, is of less value as a guide to decision making for PMTCT policy and programming in LMICs. Overall, review evidence to guide LMIC PMTCT program planning remains limited by: lack of high quality studies; focus of past reviews on limited portions of the PMTCT cascade and/or focus on HIV care in general rather than PMTCT specifically; and inclusion of high income country studies where the context of PMTCT care is often substantially different than in LMICs.

This review was developed in collaboration with knowledge users from the Malawi Ministry of Health's HIV treatment and care technical working group. The objective of this current review was to identify what interventions at the patient, provider, or health system level are effective compared to no intervention or usual care in improving uptake and retention of HIV-positive mothers and their infants in PMTCT services. Given the unique challenges facing PMTCT health services in LMICs, this review is targeted to provide guidance for PMTCT policy and programming in LMICs, and therefore included a broad range of intervention categories, as well as, both maternal and infant outcomes from across the spectrum of the PMTCT cascade.

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). 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

results could be abstracted. No restriction was placed based on language of publication, publication status, study time frame, or duration of follow-up.

Information Sources and Literature Search:

A search strategy was developed in consultation with an experienced information specialist (MA) and peer reviewed by 2 additional information specialists (EC, BS) using the Peer Review of Electronic Search Strategies checklist (22). The following databases were searched from inception to July 31, 2015 and subsequently updated using the same search strategy for the period July 31, 2015 to January 15, 2018, using MeSH headings and text words related to HIV, pregnancy, breastfeeding, mother to child transmission, interventions, treatment uptake and retention, and low- and middle-income countries: MEDLINE, EMBASE, The WHO Global Health Library, CAB abstracts, EBM Reviews, CINAHL, HealthSTAR, Web of Science, Scopus, PsychINFO, POPLINE, ERIC, NLM gateway, LILACS, Google Scholar, DARE, ProQuest Dissertation & Theses and Sociological abstracts, OpenGrey, The Cochrane Library, WHO International Clinical Trials Registry, Controlled Clinical Trials, and clinicaltrials.gov. Several databases planned for inclusion in our search were no longer available or not accessible by our group at the time of the search and were therefore not included: AIDS Education Global Information System, British Library Catalogue, and the New York Academy of Grey Literature. In addition, we searched reference lists of included articles, and contacted several experts in the field to inquire about eligible unpublished or in progress studies. See supplementary file for complete MEDLINE search strategy.

Study Selection and Data Collection Process:

A screening checklist was developed and piloted by 2 authors (LPR, MvL) independently on a sample of 50 citations prior to screening, with 2 rounds necessary to reach >90% agreement. Two authors (LPR, MvL) then independently screened citations in 2 phases; first the titles, then abstracts were screened, and second, the full-text articles were screened. Translation software was utilized to screen articles at the titles and abstracts level, with no non-English articles remaining at the full article review phase. A data abstraction form was created using the EPOC data collection form (17) and a calibration exercise done by 2 authors to ensure consistency in screening and data extraction. A calibration exercise was conducted with completed data extraction forms compared and discussed for each of the first 3 articles to ensure consistency; data extraction was then completed for the remaining articles independently and in duplicate by 2 authors, and discrepancies resolved by consensus (LPR, MvL). Information abstracted from each study included: population, intervention, comparator, context, outcomes, study design, time frame, and appropriateness of analysis (adjustment for design effect). The primary outcomes were percentage of HIV-positive women receiving or initiated on ART prophylaxis or treatment, percentage of infants born to HIV-positive mothers receiving or initiated on ART prophylaxis, and percentage of women and infants retained in PMTCT care/completing the ART regimen as defined by the PMTCT regimen utilized (18). Secondary outcomes included: percentage of infants completing post-exposure HIV testing 4-6 weeks after birth and percentage of infants completing post-exposure HIV testing 6 weeks following termination of breast feeding for all infants with known HIV exposure; percentage of HIV exposed infants testing positive for HIV; adverse events; major or minor congenital malformations; small for gestational age; pre-mature delivery; still birth; and infant death within first 2 years of life (18).

When necessary to clarify published data or to obtain unpublished data, we contacted primary authors of studies meeting inclusion criteria. Authors were contacted by email on 2 occasions, and given 1 month to respond. Ten authors (11 reports) were contacted when data needed to calculate risk ratios were not available in the publication. Three responded and provided the requested data, 6 could not be reached, and 1 replied but was unwilling to share the additional data as they were submitting the manuscript for publication.

Methodological Quality/Risk of Bias Appraisal:

Risk of bias was assessed for each study in duplicate by 2 authors (LPR, MvL) using the Cochrane EPOC criteria for assessing risk of bias (17). Given the small number of studies included in the meta-analysis, risk of publication bias could not be examined using funnel plots. Selective reporting bias was assessed through review of trial registrations where available and categorized as unclear if not registered.

Data Synthesis:

Interventions were classified independently by 2 authors (LPR, MvL) using the EPOC taxonomy for health system interventions and discrepancies resolved through discussion (23). Clinical heterogeneity was determined based on patient, intervention, and outcome characteristics. Descriptive synthesis of study results were conducted for all studies, and are reported narratively and in tabular form. Where appropriate, random effects meta-analysis was conducted to estimate intervention effects using the Metafor Package in the statistical software R (24). Statistical heterogeneity was examined using the I^2 statistic, with $I^2 \geq 75\%$ indicating significant heterogeneity (16).

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).

Study Characteristics:

Study characteristics are outlined in Table .

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 ≥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 • Maternal age (mean): I = 29.3, C = 29.7	1) ART during pregnancy 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 ≥18 and at least 32 weeks gestation	PMTCT providers trained to prepare and counsel women on how to	Usual care	• Self-management • 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 478 couples	• % HIV positive: At post-intervention, 35% (n = 82) of female participants were HIV positive • Maternal age (mean): I = 28.3; C = 28.1	1) ART detected in mother blood samples at birth 2) ART detected in infants blood at birth 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 2) Uptake of PMTCT services through to 6 weeks postpartum 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 • Educational meetings	1200 patients	(mean):(I = 26.5; C = 26.5	the 28th week of pregnancy (AZT or HAART) 2) ART during labor (AZT or HAART 3) NVP or HAART during labor 4) Infant NVP at birth 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 2444 Patients	% HIV positive at enrollment: 33% overall	NVP in cord blood
Dryden-Peterson; 2015	Provider/System	Stepwedge 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 • Educational meetings	19 Clusters 336 women	% HIV positive: I = 189 (47.6%) and C= 177 (44.6%) • Maternal age (median): (I = 28; C = 29	ART initiation by 30 wks gestation

					women eligible for ART initiation					
Mwapasa; 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 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 • The use of information and communication technology	30 Clusters 1350 women	• Maternal age (median): MIP = 29.5; MIP+SMS = 29.2; SOC = 29.4	1) Maternal retention in care at 12 months postpartum trial data 2) Infant retention in care at 12 months postpartum trial data 3) Maternal retention in care at 12 months using MOH definition 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	• Continuous quality improvement	32 Clusters: (6 later excluded) 532 women (21 withdrew leaving 511 in total)	• Maternal age (median): I = 27 ; C = 27	1) ART initiated within 2 week of enrolment 2) Retention in care at 6 months 3) Infants starting prophylaxis within 72 hours 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. 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 • The use of information and communication technology	21 Clusters 1269 women	• Maternal age (median across all 3 arms): 27	1) ART uptake 2) Retained in care at 1 year: 3) Retained in care at 2 years trial data 4) Retained in care at 2 years MOH definition 5) Infant HIV tested at 6 weeks 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.					
Tomlinson; 2014	Provider/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 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.	• Role expansion or task shifting • Outreach services	30 Clusters 3957 women	Maternal age (median): I = 23; C = 23	1) Infant HIV testing by 6 weeks 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.	• Role expansion /task shifting Integration • Packages of care	12 Clusters 369 patients	• Maternal age (median): I = 26 ; C = 28	1) Maternal ART initiation 2) Maternal-infant retention in care at 6 week postpartum 3) Maternal-infant retention in care at 12 weeks post partum

				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	• Integration • Educational meetings	6 Clusters	Not available	1) ART in labor: 2) Infants receiving prophylaxis within 48 hours 3) Infant HIV-positive
Killam; 2010	System	Stepwedge 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	• Integration	8 Clusters 31536 patients	• % HIV positive: I = 21.8%; C = 22.2% • Maternal age (mean): I = 27.5; C = 27.3	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	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	• The use of information and communication technology	388 Patients	• % HIV positive: 29.3% (388/1324) • 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+)	1) Maternal postpartum clinic attendance to 8 weeks 2) Infant HIV testing by 8 weeks

				mobile phone	after delivery					
Rotheram-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	• Role expansion or task shifting • Outreach services	26 Clusters: (2 later removed); 1144 eligible women	• %HIV positive: I = 149 (25.5%); C =146 (26.7%) • Mean maternal age : I = 26.5; C = 26.3	1) ART prior to labor 2) AZT or HAART during labor 3) NVP or HAART at onset of labor 4) Infant prophylaxis within 24 hours of birth 5) AZT dispensed for infant and medicated as prescribed 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 1876 patients	Not available	1) ART in pregnancy 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	Non-integrated ANC clinics provided routine PMTCT services and referred HIV-positive pregnant women	• Integration	12 Clusters: 1172 women	• %HIV positive: I = 48.5%, C = 51.5% • Maternal age (mean): I = 25.0, C = 24.8	1) ART during pregnancy 2) ART during Labor 3) ART after birth 4) Infant ART after

					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

The studies included 14 cluster RCTs with parallel study design, 2 cluster RCTs with step-wedge design, and 2 RCTs. The number of clusters ranged from 6 to 40, and participants across all study types ranged from 160 to 31,536. All included studies were conducted in Sub-Saharan Africa between 2005 and 2016. Half of included studies reported multifaceted interventions including 2 or more EPOC category components [9/18] and as a result several were categorized at more than 1 intervention level: patient [4], provider [1], system [7], patient/provider [1], or provider/system [5]. Interventions directed all or in part to the health system level were most

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

Reporting of population characteristics varied widely across studies as did outcome definitions. Seven studies limited participation to pregnant women 17-18 years of age or older; median ages across the studies ranged from 23 to 29.7 years. Marital status was reported in 14 studies, and varied widely from 9% to 99% of women who were married or had a live-in partner. Maternal education level was reported in 12 studies; 5 studies reported the majority of women having no or primary education, 5 studies reported the majority of women having received secondary education, and, 2 reported mean/median years of education [10.3 years, 10 years [range 8-12years]]. Maternal employment [6/18] and parity [2/18] status were reported in a minority of studies (Table 1). No pre-specified adverse events were reported in the identified studies.

Reported outcomes varied substantially across studies, with few studies within intervention categories reporting comparable outcomes. For example, 5 studies reported interventions employing integration alone [2] or in combination with other interventions [3], with only 1 PMTCT outcome in common among the 2 studies employing integration alone. The most commonly reported outcomes were maternal ART use during pregnancy and labor and delivery, infant prophylaxis at birth, and infant HIV testing at 6-8 weeks.

As a result of the multifaceted nature of the majority of interventions employed, and variability in PMTCT outcomes reported, the ability to combine results statistically was limited.

Methodological Quality:

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

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

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

Descriptive Synthesis:

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

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%) 2) Retention in care at 6-8 week postpartum: 33/41(81%)	1) ART during pregnancy: 12/32 (50%) 2) Retention in care at 6-8 week postpartum: 28/32(88%)	1) 1.56 (0.93 - 2.62) 2) 0.92 (0.75-1.12)	1) AOR 2.8 (1.02-4.79) 2) AOR 0.39 (0.04-3.99)
Reynolds; 2010	Patient	• Self-management • 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%) 2) ART detected in infants blood at birth: 12/13 (92%) 3) Infant HIV positive at 6 weeks:1/30 (3.3%)	1) ART detected in mother blood samples at birth: I6/12 (50%) 2) ART detected in infants blood at birth: 9/12 (75%) 3) Infant HIV positive: 3/39 (7.7%)	1) 1.50 (0.78-2.88) 2) 1.23 (0.86-1.77) 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%) 2) Uptake of PMTCT services through to 6 wks postpartum:146/216 (67.6%) 3) HIV positive infants at 6 weeks: 5/169 (3.0%)	1) Retention in care at 6 weeks postpartum: 157/217 (72.4%) 2) Uptake of PMTCT services through to 6 wks postpartum: 116/217 (53.5%) 3) HIV positive infants at 6 weeks: 6/156 (3.9%)	1) 1.11(1.00-1.23) 2) 1.26(1.08-1.48) 3) 0.77(0.24-2.47)	1) ARD 1.13 (1.02-1.26) 2) ARD 1.31 (1.12-1.54) 3) –
Richter, 2014	Patient/Provider	• Role expansion or task shifting • Education	Peer Mentor led educational meetings	Usual Care	1) ART from the 28th week of pregnancy (AZT or HAART): 340/377 (90.2%) 2) ART during labor (AZT or HAART):	1) ART from the 28th week of pregnancy (AZT or HAART): 455/466 (95.5%) 2) ART during labor (AZT or	1) 0.92 (0.89-0.96)	1) AOR 0.44 (0.26,0.74) 2) AOR 1.16(0.44, 3.02)

		al meetings			282/377 (74.8%); 3) NVP or HAART during labor: 361/377 (95.8%) 4) Infant NVP at birth: 364/377 (96.6%) 5) AZT dispensed for infant and medicated as prescribed: 348/377 (92.3%)	HAART): 334/466 (71.7%) 3) NVP or HAART during labor: 456/466 (97.9%) 4) Infant NVP at birth: 451/466 (96.8%) 5) AZT dispensed for infant and medicated as prescribed: 374/466 (80%)	2) 1.04 (0.96-1.13) 3) 0.98 (0.95-1.00) 4) 1.00 (0.97-1.02) 5) 1.15 (1.09-1.21)	3) AOR 0.53 (0.20, 1.41) 4) AOR 1.00 (0.36, 2.79) 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-Peterson; 2015	Provider/System	• The use of information and communication technology • 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)
Mwapasa; 2017	Provider/System	• Integration • The use of information and communication technology	MIP= integration of antenatal and HIV care, routine patient tracing 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%) MIP+SMS 115/493(23.3%) 2) Infant retention in care at 12 months postpartum trial data: MIP 32/386 (8.3%) MIP+SMS 82/399 (20.1%) 3) Maternal retention in care at 12 months using MOH definition: MIP 334/461 (72.4%) MIP+SMS 332/493 (67%) 4) Infant retention in care at 12 months using MOH definition: MIP 291/386 (75.4%) MIP+SMS 323/399 (80.9%)	1) Maternal retention in care at 12 months postpartum trial data: SOC 90/396 (22.7%) 2) Infant retention in care at 12 months postpartum trial data: SOC 32/300 (10.7 %) 3) Maternal retention in care at 12 months using MOH definition: SOC 274/396 (69.1%) 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) 2) MIP vs SOC 0.78 (0.49-1.24), MIP+SMS vs SOC 1.93 (1.32-2.82) 3) MIP vs SPC 1.05(0.96-1.14), MIP+SMS vs SOC 0.97(0.89-1.06) 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) 2) MIP vs SOC ARR 0.89 (0.31-2.58), MIP+SMS vs SOC ARR 1.40 (0.85-2.31) 3) MIP vs SPC ARR 1.05 (0.93-1.18), MIP+SMS vs SOC ARR 0.99 (0.93-1.05) 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/System	• Continuous quality improvement	QI teams established, coaching, and collaborative meetings	Routine MOH support	1) ART initiated within 2 week of enrolment: 261/264 (98.9%) 2) Retention in care at 6 months. 117/264 (44.3%) 3) Infants starting prophylaxis within 72 hours : 138/209 (66**%)** 4) Infant HIV testing at 6-10 weeks 102/209 (48.8%)	1) ART initiated within 2 week of enrolment: 233/247 (94.3%) 2) Retention in care at 6 months. 102/247 (41.3%) 3) Infants starting prophylaxis within 72 hours 145/194 (74.7%) 4) Infant HIV testing at 6-10 weeks: 49/194 (25.3%)	1) 1.05 (1.01-1.08) 2) 1.07 (0.88-1.31) 3) 0.88 (0.78-1.00) 4) 1.93 (1.46-2.55)	1) -- 2) ARR 1.08(0.78, 1.49) 3) ARR 0.95 (0.84, 1.07) 4) ARR 1.76(1.27, 2.42)
Phiri; 2017	Provider/System	• Role expansion or task shifting outreach services • The use of information and communication technology	FBPS – facility based peer support from mentor mothers CBPS- community based peer support from mentor mothers	SOC- standard of care	1) ART uptake: FBPS- 366/428 (86%) CBPS- 355/394 (90%) 2) Retained in care at 1 year: FBPS- 277/366 (78%) CBPS- 258/355(74%) 3) Retained in care at 2 years (trial data): FBPS- 223/428(52%) CBPS- 211/394 (54%) 4) Retained in care at 2 years (MOH definition): FBPS- 298/428 (70%) CBPS- 292/394 (74%) 5) Infant HIV test at 6 weeks: FBPS- 200/289(69%) CBPS- 95/286 (68%) 6) Infant HIV positive at 6 weeks: FBPS- 1/199(1%) CBPS- 2/195 (2%)	1) ART uptake: SOC- 361/447(81%) 2) Retained in care at 1 year: SOC- 261/361 (74%) 3) Retained in care at 2 years (trial data): SOC- 169/447 (38%) 4) Retained in care at 2 years (MOH definition): SOC- 255/447(57%) 5) Infant HIV test at 6 weeks: SOC- 169/273(62%) 6) Infant HIV positive at 6 weeks: SOC- 2/169(1%)	1) SOC vs FBPS 1.06 (1.00- 1.12), SOC vs CBPS 1.12 (1.06-1.18) 2) SOC vs FBPS 1.05(0.96-1.14), SOC vs CBPS 1.01 (0.92-1.10) 3) SOC vs FBPS 1.38(1.19-1.60), SOC vs CBPS 1.42 (1.22-1.65) 4) SOC vs FBPS 1.22(1.10-1.35), SOC vs CBPS 1.30 (1.18-1.43) 5) SOC vs FBPS 1.12 (0.99-1.26), SOC vs CBPS 1.23 (1.11-1.38) 6) SOC vs FBPS 0.42 (0.04-4.64), SOC vs CBPS 0.87 (0.12-6.09)	1) ARD 0.06(-0.03, 0.15), ARD 0.09 (0.01,0.18) 2) ARD 0.06(-0.06,0.18), ARD 0.08(0.04, 0.20) 3) ARD 0.13(-0.01, 0.26), 0.16 (0.03, 0.30) 4) -- 5) -- 6) ---
Tomlinson: 2014	Provider/System	• Role expansion or task shifting • Outreach services	10 structured home visits from community health workers addressing PMTCT and newborn care	3 home visits from community health workers providing support in accessing social welfare grants	1) Infant HIV testing by 6 weeks: 420/571(73.6%) 2) Infant HIV positive at 12 weeks: 28/568 (4.9%)	1) Infant HIV testing by 6 weeks: 465/698(66.6%) 2) Infant HIV positive at 12 weeks: 32/697 (4.6%)	1) 1.10 (1.03-1.19) 2) 1.07 (0.65-1.76)	1) ARR 1.10 (0.97, 1.25) 2) ARR 1.07 (0.69,1.66)

Aliyu; 2016	System	• Role expansion /task shifting Integration • Packages of care	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%) 3) Maternal-infant retention 12 weeks post partum: 112/150pairs (75%)	1) Maternal ART initiation for PMTCT: 77/197 (39%), 2) Maternal-infant retention in care at 6 weeks postpartum: 15/170 pairs (9%) 3) Maternal-infant retention 12 weeks post partum: 11/168 pairs (7%)	1) 2.47 (2.07-2.95) 2) 9.44 (5.60-15.40) 3) 11.40 (6.40-20.34)	1) ARR 3.3 (1.4-7.8) 2) ARR 9.1 (5.2-15.9) 3) ARR 10.3(5.4-19.7)
Geelhoed; 2013	System	• Integration • Educational meetings	Integrated maternal child health and HIV care	Usual Non-integrated care	1) ART in labor: post intervention:112/121 (93%) 2) Infants receiving prophylaxis within 48 hours: post intervention: 117/126 (93%); 3) Infants HIV-positive: post intervention: 9/123 (7%)	1) ART in labor: intervention phase =93/96(97%) 2) Infants receiving prophylaxis within 48 hours: intervention phase: 95/95(100%) 3) Infants HIV positive: intervention phase: 7/60(12%)	1) 0.96 (0.90-1.02) 2) 0.93 (0.88-0.97) 3) 0.63 (0.25-1.60)	-- -- --
Killam; 2010	System	• Integration	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; 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%) 2) Infant HIV testing by 8 wks: I172/187 (92.0%)	1) Maternal postpartum clinic attendance: 22/187 (11.8%) 2) Infant HIV testing by 8 wks: 154/181 (85.1%)	1) 1.66 (1.03-2.70) 2) 1.08 (1.00-1.16)	-- -
Rotheram-Borus; 2014	System	• Role expansion or task shifting • Outreach services	Antenatal and postnatal home visits from community health workers	Usual care	1) ART prior to labor: 169/179 (94.4%) 2) AZT or HAART during labor: I164/179 (91.6%) 3) NVP or HAART at onset of labor: 166/179 (92.7%) 4) Infant prophylaxis within 24 hours of birth: 171/179 (95.5%) 5) Infant ART after birth: 172/179 (96.1%) 6) Infant HIV testing at 6 weeks: 155/160 (96.9%)	1) ART prior to labor: 149/159 (93.7%) 2) AZT or HAART during labor: 147/159 (92.5%) 3) NVP or HAART at onset of labor: 142/159 (89.3%) 4) Infant prophylaxis within 24 hours of birth: 141/159 (88.7%) 5) Infant ART after birth: 142/159 (89.3%) 6) Infant HIV testing at 6 weeks: 132/140 (94.3%)	1) 1.01 (0.95-1.06) 2) 0.99 (0.93-1.06) 3) 1.04 (0.97-1.11) 4) 1.08 (1.01-1.15) 5) 1.08 (1.01-1.14) 6) 1.03 (0.98-1.08)	1) AOR 1.08 (0.42, 2.80) 2) AOR 0.87 (0.39, 1.95) 3) AOR 1.52(0.70, 3.31) 4) AOR 2.94(1.41, 6.12) 5) AOR 2.95 (1.12, 7.73) 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%) 2) Infant HIV tested by 6-8 wks: 283/604.4 (47%)	1) ART in pregnancy: 664/1037(64%) 2) Infant HIV tested by 6-8 wks: 270/710.6 (38%)	1) 1.07 (1.00-1.14) 2) 1.23 (1.09-1.40)	-- --
Turan; 2015	System	• Integration	Integrated HIV and antenatal care	Usual, non-integrated care	1) ART during pregnancy: 138/173 (80%) 2) ART during Labor: 28/173 (16%) 3) ART after birth: 22/173 (13%) 4) Infant ART after birth: 50/173 (29%) 5) ART throughout all 3 PMTCT periods: 37/176 (21.0%) 6) Infant HIV testing before 3 months: 143/569 (25%) 7) Infant HIV testing at 9 months: 361/569 (63%) 8) Infants HIV tested by 6 weeks: 143/568 (25%) 9) Infants HIV positive at 6 weeks: I6/143 (4.2%) 10) Infants HIV tested by end of study (up to 12 m): 382/568 (67.3%) 11) Infants HIV positive at 9 months: 28/382 (7.3%)	1) ART during pregnancy: 75/152 (49%) 2) ART during Labor: 84/152 (55%) 3) ART after birth: 57/152 (38%) 4) Infant ART after birth: 106/152 (70%) 5) ART throughout all 3 PMTCT periods: 23/153 (15.0%) 6) Infant HIV testing before 3 months: 106/603 (18%) 7) Infant HIV testing at 9 months: 326/603 (54%) 8) Infants HIV tested by 6 weeks: 106/594 (18%) 9) Infants HIV positive at 6 weeks: 7/106 (6.6%) 10) Infants HIV tested by end of study (up to 12 m): 338/594 (57.0%) 11) Infants HIV positive at 9 months: 27/338 (8.0%)	1) 1.61 (1.35-1.93) 2) 0.29 (0.20-0.42) 3) 0.34 (0.22-0.53) 4) 0.41 (0.32-0.54) 5) 1.40 (0.87-2.24) 6) 1.43 (1.14-1.79) 7) 1.17 (1.07-1.29) 8) 1.41 (1.13-1.76) 9) 0.64 (0.22-1.84) 10) 1.18 (1.08-1.29) 11) 0.92 (0.55-1.53)	1) AOR 4.05 (2.0, 8.0) 2) AOR 0.16 (0.04, 0.68) 3) AOR 0.24 (0.08, 0.70) 4) AOR 0.18 (0.09, 0.35) 5) AOR 1.72 (0.85, 3.48) 6) AOR 1.57 (0.61,4.07) 7) AOR 1.47 (0.76,2.86) 8) AOR 1.57 (0.61-4.07) 9) AOR 0.62 (0.20,1.98) 10) AOR 1.45 (0.71,2.82) 11) AOR 0.89 (0.56,1.43)

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: The use of information and communication technology	Facility based peer support from mentor mothers arm Community based peer support from mentor mothers arm	355/394 (90%) 366/428 (86%)	361/447(81%)	1.06 (1.00-1.12), 1.12 (1.06-1.18)*
	Aliyu; 2016	Role expansion/task shifting Integration: 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: 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: 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)**
ART in Labor & Delivery	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%)	I6/12 (50%)	1.50 (0.78-2.88)
	Richter, 2014	Role expansion or task shifting: Educational meetings	Peer led education meetings	282/377 (74.8%); 361/377 (95.8%)	334/466(71.7%); 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	I164/179 (91.6%); 166/179 (92.7%)	147/159 (92.5%) 142/159 (89.3%)	0.99 (0.93-1.06) 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)**
ART in post-	Turan; 2015		Integration of ANC and HIV services	22/173 (13%)	57/152 (38%)	0.34 (0.22-0.53)**

partum period						
ART across the PMTCT cascade	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)
Infant Prophylaxis at birth	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%); 348/377 (92.3%)	451/466(96.8%); 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)**
Infant HIV testing at 6-10 weeks	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	I172/187 (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 Community based peer mentor support arm	200/289(69%) 95/286 (68%)	169/273(62%)	1.12 (0.99-1.26) 1.23 (1.11-1.38)*
Infant HIV Positive at 6 weeks	Turan; 2015	Integration	Integration of ANC and HIV services	I6/143 (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 Community based peer mentor support arm	1/199(1%) 2/195 (2%)	2/169(1%)	0.42 (0.04-4.64) 0.87 (0.12-6.09)
Retention in care at 6-8 weeks	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 Integration: 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)
Retention in care at 12 months	Mwapasa; 2017	Integration: The use of information and communication technology	Integration of ANC and HIV care and routine patient tracing arm Integration of ANC and HIV care and SMS enhanced patient tracing arm	89/461 (19.3%) M 334/461(72.4%)M 32/386 (8.3%) I 291/386 (75.4%) I 115/493(23.3%) M 332/493 (67%) M 82/399 (20.1%) I 323/399 (80.9%) I	90/396(22.7%)M 274/396(69.1%)M 32/300 (10.7 %) I 234/300 (78.0%) I	0.85(0.65-1.10)M 1.05(0.96-1.14)M 0.78 (0.49-1.24)I 0.97 (0.89-1.05) I 1.03(0.81-1.31)M 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: The use of information and communication technology	Facility level peer mentor support arm Community based peer mentor support arm	277/366 (78%) 258/355(74%)	261/361 (74%)	1.05(0.96-1.14) 1.01 (0.92-1.10)*
Retention in care at 24 months	Phiri: 2017	Role expansion or task shifting outreach services: The use of information and communication technology	Facility level peer mentor support arm Community based peer mentor support arm	223/428(52%) 298/428 (70%) 211/394 (54%) 292/394 (74%)	169/447 (38%) 255/447(57%)	1.38(1.19-1.60) 1.22(1.10-1.35)* 1.42 (1.22-1.65)* 1.30 (1.18-1.43)*

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

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

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

Patient Level Interventions:

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

Women in the intervention group were found to be significantly more likely to complete linkage to care and receive ARTs during pregnancy (RR 1.56 [95% CI 0.93-2.62]; AOR=2.8 [95% CI 1.02-4.79]), but no difference was identified between groups in accessing care at 6-8 weeks postpartum. Reynolds et al. (28) included 10 clusters and 203 patients in a study that provided pre-packaged syringes of infant nevirapine (NVP) doses to be given by mothers who delivered at home; no difference was found in the proportion of infants receiving NVP after delivery. Weiss et al. (29) included 12 clusters and 239 couples and evaluated a couples'-based PMTCT intervention compared to standard care. They found no statistically significant difference in PMTCT regimen adherence defined as ART detected in mothers blood, ART detected in infant blood, or in the rate of infant HIV infection. Yotebieng et al. (30) included 433 patients and evaluated whether conditional cash transfers improved adherence, acceptance of and retention in PMTCT services to 6 weeks postpartum. They found women in the intervention group were significantly more likely to be retained in care (RR= 1.11 [95% CI 1.00-1.23]), and to have attended all clinic visits and to have accepted recommended PMTCT services (RR= 1.26 [95% CI 1.08-1.48]). No difference was found in infant HIV positive rates at 6 weeks.

Patient/Provider Level Interventions:

One study, Richter (2014) included 8 clusters and 1200 patients and reported an intervention directed at both patients and providers in which peer mentors were trained to provide in person education sessions for patients. Risk of bias was rated as high or unclear on 5 of 6 criteria (31). They found patients in the intervention group were significantly less likely to adhere to ARTs during pregnancy (AZT or HAART) (RR= 0.92 [95% CI 0.89-0.96]; AOR= 0.44 [975% CI 0.26-0.74]). No statistically significant effects were found on the remaining outcomes including: ART

use during labor and delivery, NVP or HAART during, infant NVP at birth, and infant ART post-birth/breast feeding. Although participants were reassessed at 6 and 12 months, we were unable to reach authors for additional information on long term outcomes.

Provider Level Interventions:

Kieffer et al. (32) included 6 clusters and 2444 patients and evaluated the impact of a 1-day PMTCT knowledge and skills training course for nurses and midwives compared to standard training alone (no intervention); risk of bias was rated high or unclear on 5 of 6 criteria. They found a statistically significant increase in the proportion of women with ART detected in cord blood as a marker of ART use during labor and delivery (RR= 1.17 [95% CI 1.08-1.26]).

Provider/System Level Interventions:

Five studies reported interventions directed at both the provider and health system level (33,34,35,36,37). Risk of bias ranged from 2 to 5 of 6 criteria rated as high or unclear. Dryden-Peterson et al. (33) included 19 clusters and 366 patients and provided staff training, automated transmission of HIV test results to clinic staff via short message service (SMS), and ongoing support to ante-natal clinics (i.e. education for new staff, supporting SMS printers, monitoring and addressing clinic underperformance). There was a trend towards an increase in the proportion of mothers initiated on ARTs by 30 weeks gestation in the intervention group.

Mwapasa et al. (34) conducted a 3-arm cluster RCT with 30 clusters and 1350 patients to assess the impact of 2 different patient tracing methods routine paper (MIP) and SMS triggered tracing (MIP+SMS) combined with integrated care against standard care (SOC). They found no

significant difference in maternal retention in care at 12 months in either intervention group relative to controls using study definitions, or ministry of health definitions for retention. They found no statistically significant difference in infant retention in care at 12 months in either intervention group relative to controls using study definitions, or ministry of health definitions for retention .

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

Phiri et al. (36) conducted a 3-arm cluster RCT with 21 clusters and 1269 women evaluating facility-based peer support (FBPS) and community-based peer support (CBPS) from expert mothers against standard of care (SOC). They found non-significant improvement with FBPS and small statistically significant improvements with CBPS in uptake of ARTs (RR= 1.12 [95% 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 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 1.22-1.65]; ARD=0.16 [95% CI 0.03-0.30]), relative to SOC. Retention in care at 2 years was significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-1.43]) using ministry of health definitions for retention in care. Infant HIV testing at 6 weeks was

significantly higher in the CBPS only (RR=1.23 [95% CI 1.11-1.38]). There was no difference in infant HIV positive rates at 6 weeks in either intervention group.

Tomlinson et al. (37) included 3957 patients in 30 clusters and evaluated the impact of increased training of community health workers and increased home visits by community health workers during and post delivery to provide PMTCT counselling and newborn care. They found a significantly increased proportion of infants receiving HIV testing at 6 weeks in the intervention group (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) and no difference in mother to child HIV transmission at 12 weeks.

System Level Interventions:

Seven studies reported interventions at the system level (38,25,39,40,41,24,42). Risk of bias ratings for system level intervention studies ranged from 2 to 5 of 6 criteria rated as high or unclear risk of bias. Aliyu et al. (38) evaluated an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community involvement through male champions, compared to standard care across 12 clusters and 369 patients. They found significant improvement in the proportion of eligible women 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 retention of mother-infant in care at 6 weeks (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) and 12 weeks postpartum (RR=11.40 [95% CI 6.40-20.34]; ARR= 10.3 [95% CI 5.4-19.7]).

Geelhoed et al. (39) included 6 clusters and 217 patients in the post intervention period and evaluated the impact of integration of HIV and maternal child health services during both antenatal and postnatal periods. They found no improvement in the proportion of women receiving ARTs during labor and delivery, proportion of infants receiving prophylaxis within 48 hours and the proportion of HIV positive infants.

Killam et al. (26) assessed the impact of integration of antenatal and HIV care relative to usual care (antenatal and HIV care separate) in 8 clusters and 31,536 patients. They found a statistically significant increase in the proportion of eligible women receiving ARTs during pregnancy, (RR= 2.28 [95% CI 1.86-2.80]; AOR= 2.01 [95% CI 1.37-2.95]).

Odeny et al. (40) evaluated use of automated SMS messages to patients (n= 388) during pregnancy and post-delivery. They found statistically significant improvements in maternal antenatal clinic attendance (RR= 1.66 [95% CI= 1.03-2.70]) and infant HIV testing by 8 weeks (RR= 1.08 [1.00-1.16]).

Rotheram-Borus et al. (41) assessed the impact of home visits by community health workers in addition to clinic care in 24 clusters and 1144 patients. They found significant improvement in the proportion of infants receiving NVP within 24 hours of birth (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.94 [95% CI 1.41-6.12]) and AZT dispensed for infant and used as prescribed in the intervention group (RR= 1.08 [95% CI 1.01-1.14]; AOR 2.95 [95% CI 1.12-7.73]). There was no significant difference in maternal AZT/HAART use prior to labor, or during labor; maternal NVP/HAART use at onset of labor; and infant 6-week HIV testing relative to controls.

Rustagi et al. (42) evaluated a systems analysis and improvement intervention across 36 clusters in 3 countries, including 1876 patients. They found no significant improvement in the proportion of pregnant women receiving ARTs (RR= 1.07 [95% CI 1.00- 1.14]) or infants tested for HIV by 6-8 weeks (RR= 1.23 [95% CI 1.09-1.40]).

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

Descriptive synthesis of findings according to PMTCT outcomes:

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

Overall, findings are often mixed and effect sizes small, with many of uncertain clinical significance.

Five studies found significant improvements in ART use during pregnancy ranging with RR ranging from 1.12 to 2.48 (25, 26, 27, 36, 38). Effective interventions included: integration of ANC and HIV services (RR= 1.61[(1.35-1.93] AOR= 4.05 [95% CI 2.00-8.00]) (25) and (RR= 2.28 [95% CI 1.86-2.80] AOR= 2.01 [95% CI 1.37-2.95]) (26); monthly baby showers at participating churches providing education through games, 'mama packs' containing delivery supplies, laboratory testing, and a contact point for follow-up (RR 1.56 [95% CI 0.93-2.62], AOR=2.8 [95% CI 1.02-4.79]) (27); community based peer support from mentor mothers (RR= 1.12 [95% CI 1.06-1.18], ARD 0.09 [95% CI 0.01-0.18]) (36) ; and an integrated package of PMTCT services including point-of-care CD4 testing, decentralized PMTCT care, integrated mother/infant services, and community champions, (RR= 2.47 [95% CI 2.07-2.95], ARR 3.3 [95% CI 1.4-7.8]) (38). Four studies evaluating: staff training and support to ante-natal clinics, and automated SMS transmission of HIV test results to clinic staff (33); a quality improvement initiative (35); community health worker ante- and post-natal home visits (41); and facility level systems analysis and improvement intervention (42), found no significant difference in ART use during pregnancy. One study evaluating peer mentor led educational meetings, found ART adherence during pregnancy lower in the intervention group (31).

Six studies reported ART use during labor and delivery, with 4/6 finding no significant effect (29, 31, 39, 41)), 1 finding a significant but small improvement RR=1.17 (32) and 1 finding significantly reduced ART use in the intervention group RR=1.614 (25). The one study that

found a small significant effect employed a 1-day PMTCT knowledge and skills training course for nurses and midwives (RR= 1.17 [95% CI 1.08-1.26]) (32). Ineffective interventions included; couples based PMTCT intervention (29), peer mentor led educational meetings (31), integration of maternal child health and HIV services (39), and community health worker ante-natal and post-partum home visits (41). In contrast to the findings for ART use during pregnancy, ART use during labor and delivery was low significantly lower with integration of ANC and HIV care RR=0.29 [95% CI (0.20-0.42)] AOR= 0.16 [95% CI 0.04, 0.68] (25).

Only 1 study evaluated ART use in the post-partum period and found significantly reduced ART use during this period (RR= 0.34 [0.22-0.53]; AOR=0.24 [95% CI 0.08-0.70]) with integration of ANC and HIV care (25).Two additional studies evaluated uptake across the cascade, with conditional cash transfer found to significantly improve uptake of PMTCT recommendations (RR= 1.26 [95% CI 1.08-1.48]) (30) and no difference found for integration of ANC and HIV services (25).

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

Seven studies reported infant HIV testing at 6-10 weeks. Three of 7 found significantly improved rates of infant testing by 6-10 weeks of age with RR ranging from 1.08 to 1.93 (35,37,40), 3/7 no difference (25, 41,42), and one study finding a mixed effect of peer support (36). Improvements in infant HIV testing were found for a quality improvement intervention (RR=1.93 [95% CI 1.46-2.55]; ARR= 1.76 [95% CI 1.27-2.42]) (35), increased training of and home visits from community health workers (RR= 1.10 [95% CI 1.03-1.19]; ARR 1.10 [95% CI 0.97-1.25]) (37), and SMS texts to patients both antenatally and post-delivery (RR= 1.08 [1.00-1.16]) (40). One study found mixed effects of peer support on infant HIV testing, with community based peer support found to significantly improve infant HIV testing at 6 weeks (RR=1.23 [95% CI 1.11-1.38]) and no difference found for facility based peer support (36). No difference was found for integration of ANC and HIV care (25), home visits from community health workers (41) or a facility level system analysis and quality improvement intervention (42).

Outcome definitions for retention in care and infant HIV-positive rates were highly variable, ranging from 6 weeks to 2 years for the former, and 6 weeks to 1 year for the later. As for other PMTCT outcomes noted above, relatively more short term outcomes (6 weeks) were reported for retention and infant HIV-positive rates. Three studies evaluated maternal or maternal/infant retention in care at 6 weeks, with 2 studies evaluating conditional cash transfers (30) and an integrated package of PMTCT services including point-of-care CD4 testing, decentralized care, integrated mother/infant services, and community champions (38), finding significantly improved retention (RR= 1.11 [95% CI 1.00-1.23]) and (RR= 9.44 [95% CI 5.60-15.4]; ARR=9.1 [95% CI 5.2-15.9]) at 6 weeks, and a third employing monthly baby showers finding no difference (27). Two studies examined retention in care at 1 year. One study evaluating

integration of ANC and HIV care with and without SMS enhanced tracing in a 3 arm trial and found no difference in maternal or infant retention at 1 year (34). A second study evaluated the effect of community based peer support (CBPS) and facilty based peer support (FBPS) on retention in care at 1 and 2 years, in a 3 arm trial. They found non-significant improvement with FBPS and small statistically significant improvements with CBPS in retention in care at 1 year (RR=1.01 [95% CI 0.92-1.10]) and 2 years (RR= 1.42 [95% CI 1.22-1.65]) using trail data (36). Retention in care at 2 years was significant for both FBPS (RR= 1.22 [95% CI 1.10-1.35]) and CBPS (RR= 1.30 [95% CI 1.18-1.43]) using ministry of health definitions for retention in care.

Four studies examined infant HIV-positive rates at 6-10 weeks post-partum. Evaluated interventions included; integration of ANC and HIV care (25), couples based HIV/PMTCT counselling (29), conditional cash transfers (30), and peer support (36). All found no difference.

Discussion:

Eighteen studies were included in our review. Heterogeneity of interventions and outcome reported limited both comparison across studies and intervention categories, as well as, opportunities for meta-analysis. The majority of studies were of moderate to high risk of bias, primarily due to limitations inherent to health systems research and unclear reporting of key methodological factors.

Based on our review findings, several interventions appear promising. In the single meta-analysis conducted with data from 2 studies (25,26), we found a significant increase in ART use during pregnancy with integration of HIV and antenatal care compared to standard non-

integrated care. Consistent with the findings of our meta-analysis, narrative review of 3 studies found small positive effects of integration of HIV and antenatal care, alone or as part of a complex intervention, on ART use during pregnancy. However, the effects of integration on PMTCT outcomes during labor and delivery, and post-delivery were less clear, with no difference found for some studies (39, 34) and for some outcomes (25), and one study finding reduced ART use during labor and delivery, and post-delivery (25). While the findings of Turan et al. (25) occurred in the setting of resource challenges impacting implementation and relatively low numbers of adherence reports beyond the antenatal period, this was the case for both intervention and control groups. Therefore, as integrated care is now common practice future work focusing on how integration of maternal child health and HIV care may be optimized alone or in combination with other interventions to optimize PMTCT outcomes beyond the antenatal period is needed.

Four studies evaluating different approaches to outreach services alone or in combination with other interventions found small positive effects on linkage to care, ART use during pregnancy and labor/delivery, and early infant HIV testing. Two studies found positive effects of role expansion or task shifting, in the form of peer mentorship support, on ART use during pregnancy and, when combined with outreach services, positive effects were seen on long term retention in care and early infant HIV testing. Additional strategies found to have positive effects on PMTCT outcomes, each in a single study, included: educational meetings, conditional cash transfers, continuous quality improvement, and use of information and communication technology.

An important finding of the present review is the high degree of variability in outcome definitions and relative lack of longer-term outcome data. While in some instances variability of outcome definitions may be considered a strength where both self-report and biological markers of ART use are included, variability in timing of outcomes limits comparison across studies and opportunities for meta-analysis and as a result limits the strength of conclusions and utility of the findings to PMTCT knowledge users. Although uptake and early retention in PMTCT services is clearly critical to reducing HIV transmission, longer term outcomes are equally important to understanding how retention in care can be optimized to reduce late HIV-transmission. Utility of future work would be substantially improved through both standardization of timing of PMTCT outcomes and through funding opportunities that would allow for evaluation of longer term outcomes.

In keeping with other systematic reviews focused on interventions aimed at improving PMTCT care and outcomes published to date (8,9,13,14,15), our review found the evidence base available to guide PMTCT program planning remains limited. Similar to the systematic review by Tudor Car et al. (9), which included a single study and found improved ART use in labor/delivery from integration of care, our single meta-analysis including 2 studies found a positive effect of integration on maternal ART use during pregnancy. Wekesah et al. (13) included 73 studies, only 2 of which met inclusion criteria for the present review, and they also found variable effects of non-drug interventions on both quality of care and maternal health outcomes. Geldsetzer et al. (14) included 10 articles, with 2 overlapping studies included in our review, and focused on postpartum retention of women in PMTCT and ART care. This latter review, which included both high and LMICs and a broader range of study designs, focused on a limited portion of the

PMTCT cascade. It found inconsistent effects of integration and weak evidence of phone interventions on retention in PMTCT care. Ambia and Mandala (15) focused on interventions to improve PMTCT service delivery and promote retention. Their review was conducted over a similar timeframe to the present review, however, it differs from the present review in its inclusion of high income country studies, inclusion of a range of study designs, and in its approach to categorization of interventions. Thirty-four studies were included in their review, 11 of which were included in the present review. They found weak evidence for improvement of early infant HIV diagnosis from mobile-phone based interventions and for male involvement in reducing infant HIV transmission.

Given the focus of the present review on providing evidence-based guidance to PMTCT program planners and implementers based LMICs our review differs from the reviews noted above in several ways. First, to optimize the quality of evidence we limited our review to randomized and non-randomized controlled trials and interrupted times series studies. Second, to increase the applicability of findings to LMIC implementers, we limited our review to studies conducted in LMICs. Third, we included a broad range of intervention categories and included both maternal and infant outcomes from across the spectrum of the PMTCT cascade. Finally, in order to provide information of direct relevance to implementation planning, we categorized and analyzed interventions at both the level at which they are implemented (patient, provider, system) and using the EPOC intervention classification scheme, which groups interventions based on the intervention process/activities employed.

Limitations:

While agreement on data extraction was not calculated, an initial calibration exercise was carried out to ensure consistency in data extraction. Following this, comparison of completed data extraction forms revealed few differences. Although no study was excluded for language, it is possible that use of translation software may have resulted in exclusion of an eligible study due to inaccurate translation. Additionally, while unlikely to have led to a significant difference in results, the updated search of the ERIC database was conducted in Proquest rather than EBSCO as the later was not accessible to the second information technologist.

The multifaceted nature of the majority of interventions evaluated and variability in PMTCT outcomes reported, limited our ability to combine studies statistically and to separate effective/ineffective features of the interventions. In addition, efforts to contact authors for data necessary for risk ratio calculations was ineffective in several cases. Due to the small number of studies included in the meta-analysis publication bias could not be examined. Additionally, although pre-specified in our protocol, interpretation of findings, most commonly infant HIV infection rates, are limited by lack of power to assess secondary outcomes among included studies. As 7 of the 18 studies limited participation to women 17-18 years of age or older, results may be less generalizable to younger mothers. Finally, although the EPOC search filter is designed to identify articles from all low- and middle-income countries, only articles from Sub-Saharan Africa were included in the review. Results therefore may be less generalizable to LMICs outside Sub-Saharan Africa. In addition, this finding highlights limitations in the evidence to date and where funding should be targeted for future research based on knowledge users needs.

Future Directions:

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

Conclusions:

The body of evidence synthesized in this review and in the literature to date on effectiveness of interventions to improve uptake and retention of mothers and infants in PMTCT care is limited by low quality evidence. A single meta-analysis of 2 studies employing integration of antenatal and HIV care suggested a potential for improvement of ART use during pregnancy based on

weak evidence. Overall findings are mixed and effect sizes small and of uncertain clinical significance. In order to improve the utility of evidence to program planners future studies should strive to include key outcomes across the range of the PMTCT cascade where feasible, reduce risk of bias where possible and improve reporting of key methodological factors to allow for improved assessment of risk of bias and understanding of the likely impact of risk of bias where it cannot be addressed in design.

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

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***Authors' contributions*:** LPR and MvL conceived the study. LPR and SS developed the search strategy. LPR was prepared and registered the protocol. LPR and MvL completed all stages of article screening, data abstraction, and risk of bias appraisal. LPR prepared the initial evidence tables and manuscript. LPR conducted the meta-analysis with support from BP. MCH, NER, SP, ML, and FC provided content expertise and assisted with preparation of the protocol and manuscript. All authors provided critical revision of the manuscript and read and approved the final manuscript.

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Captions for appended Tables and Figures:

Table 1: Characteristics of Included StudiesTable 2: Results of Included Studies by Level of Intervention

Table 3: Results of Included Studies by PMTCT outcome

Figure 1: PRISMA diagram of search results and screening

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

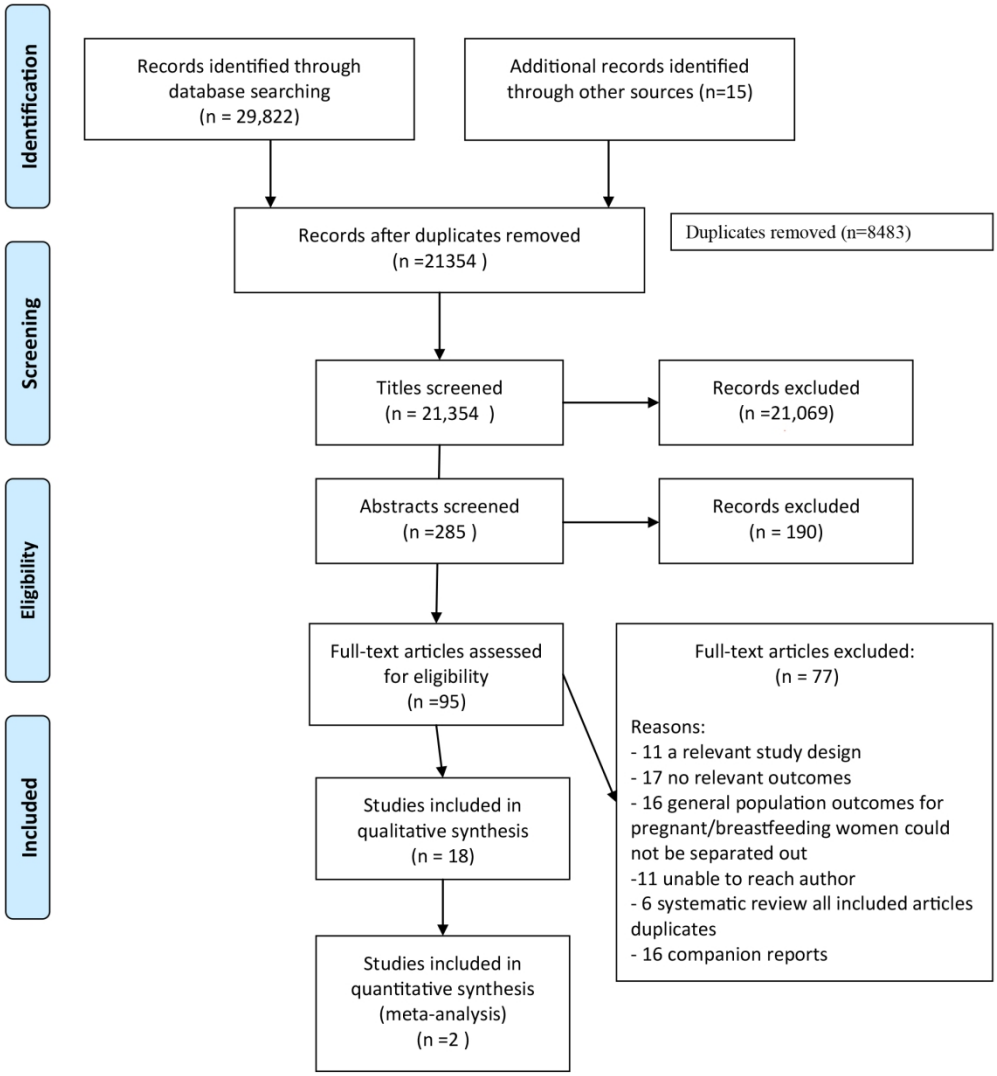


Figure 1: PRISMA diagram of search results and screening

171x184mm (300 x 300 DPI)

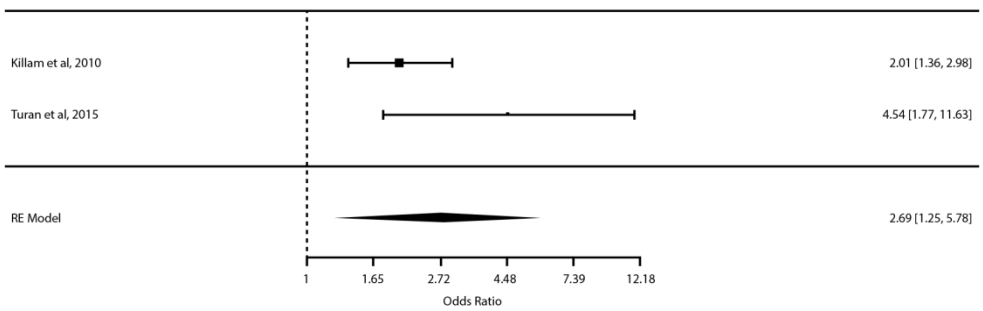
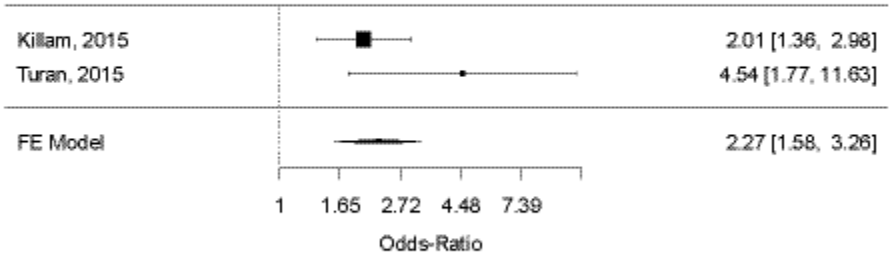


Figure 2: Forrest Plot of meta-analysis of integration of HIV and ante-natal care compared to usual (non-integrated care) effect on ART use during pregnancy

164x51mm (300 x 300 DPI)


Killam, 2015
Turan, 2015
FE Model
2.01 [1.36, 2.98]
4.54 [1.77, 11.63]
2.27 [1.58, 3.26]
1
1.65
2.72
4.48
7.39
Odds-Ratio

Search Strategy Ovid MEDLINE(R) <1946 to June Week 2 2018>:

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)

34 (breast adj2 fed*).tw,kw,kf. (5276)
35 in-utero.tw,kw,kf. (20490)
36 (intrauterine or intra-uterine).tw,kw,kf. (42420)
37 (trans-placent* or transplacent*).tw,kw,kf. (5212)
38 (f?eto-maternal or f?etomaternal).tw,kw,kf. (2682)
39 (parent* adj2 (child* or infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (28605)
40 mother*.tw,kw,kf. (147803)
41 (nursing adj2 (infant* or baby or babies or neonat* or newborn*)).tw,kw,kf. (1319)
42 (prenatal* or pre-natal*).tw,kw,kf. (70920)
43 (perinatal* or peri-natal*).tw,kw,kf. (51747)
44 (post-natal* or postnatal*).tw,kw,kf. (85370)
45 (antenatal* or antenatal*).tw,kw,kf. (23135)
46 (antepartum* or ante-partum*).tw,kw,kf. (4566)
47 (postpartum* or post-partum*).tw,kw,kf. (40829)
48 maternal*.tw,kw,kf. (172644)
49 or/1-48 (1763167)

HIV/AIDS

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)

68 (aids adj1 related).tw,kw,kf. (6614)
69 htlv*.tw,kw,kf. (11427)
70 hiv##.mp,kw,kf. (1760)
71 or/50-70 (325026)

Patient uptake / dropouts / participation
72 Patient Dropouts/ (6786)
73 exp "Patient Acceptance of Health Care"/ [includes treatment refusal MeSH] (171083)
74 exp Consumer Participation/ (32566)
75 dropout*.tw,kw,kf. (6483)
76 (uptake or up-take).tw,kw,kf. (248330)
77 (drop* adj1 out$1).tw,kw,kf. (8228)
78 (refusal* or refuse$1 or refusing).tw,kw,kf. (23366)
79 (patient* adj2 (elope or elope$1 or eloping)).tw,kw,kf. (4)
80 (non complian* or noncomplian*).tw,kw,kf. (9990)
81 complian*.tw,kw,kf. (84306)
82 (uncooperat* or unco-operat* or un-co-operat*).tw,kw,kf. (1028)
83 (cooperat* or co-operat*).tw,kw,kf. (102475)
84 (non-accept* or nonaccept*).tw,kw,kf. (592)
85 accept*.tw,kw,kf. (279089)
86 (nonparticipat* or non-participat*).tw,kw,kf. (1298)
87 participat*.tw,kw,kf. (322007)
88 (nonadher* or non-adher*).tw,kw,kf. (10638)
89 adher*.tw,kw,kf. (114637)
90 (retain* or retention*).tw,kw,kf. (244370)
91 (non-attend* or nonattend*).tw,kw,kf. (1453)
92 attend*.tw,kw,kf. (110407)
93 (comply* or complies or complian*).tw,kw,kf. (91550)
94 (non-comply* or noncomply* or non-complian* or noncomplian*).tw,kw,kf. (10004)
95 reluctan*.tw,kw,kf. (8504)
96 ((healthcare or care or advice or medical or information) adj3 seek$3).tw,kw,kf. (15252)
97 (disengag* or dis-engag*).tw,kw,kf. (2812)
98 engag*.tw,kw,kf. (82419)
99 avoid*.tw,kw,kf. (237366)
100 ut.fs. (144195)
101 ignor*.tw,kw,kf. (27215)
102 reject*.tw,kw,kf. (82472)

103 (non-embrac* or nonembrac*).tw,kw,kf. (0)
104 (un-embrac* or unembrac*).tw,kw,kf. (1)
105 (embrace* or embracing).tw,kw,kf. (7691)
106 (un-accept* or unaccept*).tw,kw,kf. (14546)
107 (unadher* or un-adher*).tw,kw,kf. (14)
108 no-show*.tw,kw,kf. (484)
109 (follow* adj1 up).tw,kw,kf. (638770)
110 incent*.tw,kw,kf. (17823)
111 enabl*.tw,kw,kf. (214935)
112 disincent*.tw,kw,kf. (859)
113 utiliz*.tw,kw,kf. (319558)
114 (inclin* or disinclin*).tw,kw,kf. (12034)
115 or/72-114 (2984236)

Study type / characteristics

116 randomized controlled trial.pt. (387105)
117 exp Randomized controlled trial/ (387132)
118 exp Randomized Controlled Trials as Topic/ (97414)
119 clinical trial.pt. (490674)
120 Double-Blind Method/ (128228)
121 Placebos/ (32662)
122 clinical trials as topic/ (171490)
123 evaluation research/ (119973)
124 program evaluation/ (47548)
125 Feasibility Studies/ (45412)
126 Pilot Projects/ (85700)
127 Evaluation Studies as Topic/ (119973)
128 Cost-Benefit Analysis/ (61646)
129 (random* or non-random* or unrandom* or nonrandom*).mp,kw,kf. (874470)
130 placebo*.mp,kw,kf. (168179)
131 rct*1.tw,kw,kf. (17367)
132 ((singl* or doubl* or trebl* or tripl*) adj1 (mask* or blind* or dumm*)).mp,kw,kf. (176744)
133 evaluat*.mp,kw,kf. (2416275)
134 effectiv*.mp,kw,kf. (1149619)
135 sustainab*.mp,kw,kf. (23041)
136 feasib*.mp,kw,kf. (177882)
137 appropriateness.mp,kw,kf. (12458)

138 efficac*.mp,kw,kf. (507876)
139 impact*.mp,kw,kf. (537916)
140 (pilot adj2 (project* or study or studies)).mp,kw,kf. (103303)
141 cost-effectiv*.mp,kw,kf. (73309)
142 (cost*1 adj2 benefit*1).mp,kw,kf. (69472)
143 (interrupt* adj2 time).mp,kw,kf. (1224)
144 or/116-143 (4705604)

Lower middle income countries
145 Developing Countries/ (63034)
146 (lmic or lmics or lami countr*).mp,sh,kf,in,jn,nj,ia,cp,pb. (534)
147 ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (106086)
148 (Afghan* or Albania* or Algeria* or Angola* or Antigua* or Barbud* or Argentin* or Armenia* or Aruba* or Azerbaijan* or Bahrain* or Bangladesh* or Barbad* or Benin* or Byelarus* or Byelorus* or Belarus* or Belorus* or Beliz* or Bhutan* or Bolivia* or Bosnia* or Herzegovin* or Hercegovin* or Botswan* or Brasil* or Brazil* or Bulgaria* or Burkina Faso* or Burkina Fasso* or Upper Volta* or Burundi* or Urundi* or Cambodia* or Khmer Republic or Kampuchea* or Cameroon* or Cameron* or Cape Verde* or Central African Republic or Chad* or Chile* or China or chinese or Colombia* or Comoros* or Comoro Islands or Comores or Mayott* or Congo* or Zair* or Costa Rica* or Cote d'Ivoire or Ivory Coast or Croatia* or Cuba* or Cyprus or cyprian or Czechoslovakia* or Czech Republic or Slovakia* or Slovak Republic or Djibouti* or French Somaliland or Dominica* or East Timor or East Timur or Timor Leste or Ecuador* or Egypt* or United Arab Republic or El Salvador* or Eritrea* or Estonia* or Ethiopia* or Fiji* or Gabon* or Gambia* or Gaza* or Georgia Republic or Georgian Republic or georgian or Ghana* or Gold Coast or Greece or greek or Grenada* or Guatemala* or Guinea* or Guam* or Guiana* or Guyana* or Haiti* or Hondura* or Hungar* or India* or Maldiv* or Indonesia* or Iran* or Iraq* or Isle of Man or Jamaica* or Jordan* or Kazakh* or Kenya* or Kiribati* or Korea* or Kosovo* or Kyrgyz* or Kirghiz* or Kirgiz* or Lao PDR or Laos* or Latvia* or Leban* or Lesotho* or Basutoland or Liberia* or Libya* or Lithuania* or Macedonia* or Madagascar* or Malagasy Republic or Malay* or Sabah* or Sarawak* or Malawi* or Nyasaland* or Mali* or Malta* or Marshall Island* or Maurit* or Agalega Island* or Mexic* or Micronesia* or Middle East* or Moldova* or Moldovia* or Mongolia* or Montenegr* or Morocc* or Ifni* or Mozambiq* or Myanmar* or Myanma or Burma* or Namibia* or Nepal* or Netherlands Antill* or New Caledonia* or Nicaragua* or Niger* or Northern Mariana Island* or Oman* or Muscat* or Pakistan* or Palau* or Palestin* or Panama* or Paragua* or Peru* or Phi?lippin* or Poland or polish or Portug* or Puerto Ric* or Romania* or Rumania* or

Roumania* or Russia* or Rwanda* or Ruanda* or Saint Kitts* or St Kitts or Nevis* or Saint Lucia* or St Lucia* or Saint Vincent* or St Vincent* or Grenadin* or Samoa* or Navigator Island* or Sao Tome* or Saudi Arabia* or saudi or Senegal* or Serbia* or Montenegr* or Seychelles or Sierra Leone or Slovenia* or Sri Lanka* or Ceylon* or Solomon Islands or Somalia* or South Africa* or Sudan* or Surinam* or Swaziland or swazi or Syria* or Tajik* or Tadjik* or Tadzhik* or Tanzania* or Thailand or thai or Togo or Togolese Republic or Tonga* or Trinidad* or Tobag* or Tunisia* or Turkey or turkish or Turkmenistan* or Turkmen* or Uganda* or Ukrain* or Urugua* or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbek* or Vanuat* or New Hebrides or Venezuela* or Vietnam* or Viet Nam* or West Bank or Yemen* or Yugoslavia* or Zambia* or Zimbabw* or Rhodesia* or cabo verd*).hw,kf,ti,ab,cp,in,jn,nj,ia,cp,pb,mp. (4641336)

149 or/145-148 (4677916)

Full topic

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

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

Full topic minus animal-only studies

152 150 not 151 (3291)

****

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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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 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 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 Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 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
DISCUSSION			
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
FUNDING			
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

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

PRISMA 2009 Checklist

doi:10.1371/journal.pmed1000097

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