Interventions for Improving Adherence and Retention in HIV-Infected Women on ART During Antenatal and Postnatal Care: A Systematic Review

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PREAMBLE

DECLARATION

I, Nikhat Hoosen hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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A heartfelt thank you to you all.

THESIS ABSTRACT

Introduction

Universal access to antiretroviral therapy (ART) during pregnancy and breastfeeding has implications for retention in HIV care and adherence to ART. Retention and adherence may be especially challenging during antenatal and postnatal periods, where women living with HIV have competing responsibilities between infant care, self-care and personal responsibilities. Lifelong ART also highlights the role interconception care (ICC) and preconception care (PCC) interventions can play in improving maternal outcomes. While the latter exist for other health topics, ICC and PCC interventions targeting women living with HIV has the potential to maintain retention in care and adherence to ART during, after, and in between pregnancies. This systematic review evaluates interventions that aim to improve retention and adherence in pregnant and postpartum women.

Methods The Cochrane Library; MEDLINE via PubMed; Web of Science; and EBSCOHOST (Africa Wide, Academic Search Premier, CINAHL, PsychArticles, Health Source Nursing Academic, PsychInfo) and conference databases were searched for articles in English published between 1990 to 2020. All study designs, intervention types and geographic locations were included. Data were extracted using a standardized tool, and effect sizes recalculated for all studies. Risk of bias was conducted using tools suited to specific study designs, and the PRECIS-2 tool assessed intervention applicability in real-world settings. The protocol was registered with PROSPERO (ID: CRD42020185196).

Results Thirty-one studies were identified, of which 31 and 16 provided retention and adherence data, respectively. No interconception or preconception care interventions were found. Interventions were predominantly from Sub-Saharan Africa, except one from the USA. Intervention types varied and included integration of services, peer support, mhealth and multicomponent interventions. The definitions of retention and adherence used for outcome assessment varied widely across studies, but almost all were scored as pragmatic in real-world settings. Due to high heterogeneity, a narrative approach was used based on study reported data and the effect sizes.

Conclusion Overall, heterogeneity of identified studies make definitive recommendations for interventions scale up difficult. Future interventions will benefit from consistent study designs, outcome definitions, outcome measurements, validated tools, and longer retention time points will strengthen the evidence base. Ongoing studies being conducted show promise in addressing some of these points.

LIST OF ABBREVIATIONS

ANC	Antenatal care
ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
ICC	Interconception care
LMIC	Low- and middle income countries
MCH	Maternal and child health
PCC	Preconception care
PHC	Primary Health Clinic
PLHIV	People living with HIV
PMTCT	Prevention of mother to child transmission
PNC	Postnatal care
VL	Viral load
WHO	World Health Organization
WLHIV	Women living with HIV

TABLE OF CONTENTS

PART A: PROTOCOL

1 INTRODUCTION

1.1 Background

Women of child bearing age account for the majority of all HIV-infected people globally (1). For HIV-infected pregnant and postpartum breastfeeding women, antiretroviral therapy (ART) use is critical to ensure maternal health and that of the newborn infant. Previously, pregnant women were either temporarily initiated on ART antepartum or at a CD4 count below 350 cells/µl. Under Option B+ and more recently universal ART for all people living with HIV, the World Health Organization (WHO) recommends pregnant women presenting for antenatal care (ANC) found to be HIV-infected, be initiated on lifelong ART regardless of CD4 count and WHO clinical stage (2). However, benefits of expanded ART access as well as virological and clinical success, depend on sustained medication adherence and retention in care of pregnant and postpartum women (3, 4). Concerns are mounting around the low levels of adherence and retention in care observed for these populations (5-7). ART non-adherence and non-retention can lead to poor outcomes such as drug resistance, disease progression to AIDS, morbidity and mortality in mothers (8-10). The risk of HIV transmission from mother to newborn during delivery, and postpartum through breastfeeding also increases if women are lost to follow-up or non-adherent to ART (2, 8).

Data from a recent systematic review (11) showed that pregnant and postpartum women in Africa have retention rates of 79.4% and 74.5%, 6 and 12 months respectively, post-ART initiation. These estimates are lower than that of the general population of adults living with HIV, in part due to the perceived and actual demands of Option B+ (11, 12). In general women also have lower ART adherence than men (13) which has been shown to be suboptimal in pregnancy with further decline during the postpartum period (8, 14, 15). Multiple and wide ranging challenges impact women's HIV medication adherence and retention during pregnancy and postpartum (4, 5, 8, 12, 16). In pregnancy pill fatigue, treatment side effects, pregnancy associated nausea (5, 17), work commitments, lack of male partner involvement (18-20) , poor maternal health due to other illnesses, stigma (17-20) and lack of money to visit health facilities have accounted for poor adherence and retention in care (5, 17). However, concern for the unborn infant is a strong facilitator for maternal ART adherence, even in the face of these obstacles (7).

Postpartum, mothers must contend with the move from concurrent maternal and in utero infant care to separate care post-delivery (3). This post-delivery transfer of HIV care is a significant de-motivator to postpartum ART adherence (4) and together with work conflicts, financial problems, clinic issues, stigma and travel to distant rural homes (3, 11) results in poor adherence and postpartum retention

in care. Another significant concern is that healthy delivery of HIV-negative infants leads to further lack of motivation for mothers remaining in care (4, 7). The latter is an important reason for lower adherence and retention postnatally compared to pregnancy.

Thus antenatal and postnatal interventions focussed on addressing these adherence challenges among others are crucial, and assessing which interventions are most successful in promoting retention in care for mothers necessary (20). Studies have highlighted the importance of targeted interventions and adaptation of programmes to improve adherence and retention in pregnant and postpartum women (3, 11).

In addition to antenatal and postnatal interventions, preconception and interconception care (PCC and ICC respectively) directed at women living with HIV (WLHIV) have the potential to influence ART adherence and retention before, during and after pregnancy. Defined as a set of interventions targeted at women and/or couples of childbearing age, regardless of pregnancy status or desire, pre-pregnancy or between pregnancies, to improve health outcomes for women, newborns and children (21), PCC and ICC for HIV-infected individuals are more focused. This takes the form of promotion of safer conception between serodiscordant couples, planned pregnancies, and preventions of HIV vertical transmission between the mother and infant (22).

1.2 Rational for the review

Existing systematic reviews on HIV medication adherence and retention in these populations have had limited inclusion criteria considering: restricted geographical locations (5, 11, 20); fewer study designs (23); the postpartum period only (16) or lack differentiation between pregnancy and postpartum (11); and outcome measures and definitions of adherence which exclude viral load (16, 20). Moreover, the search end date of these reviews are outdated being more than 2 years old (5, 16, 20, 23) and none focus on PCC or ICC. The current review aims to analyse the most recently available studies, which will include conference abstracts to ensure up to date data. Study design selections will be expanded beyond randomised control trials and cohort studies; no geographical limitations will be applied; viral load as an outcome will be incorporated; and adherence and retention definitions will be increased to include multiple types of measures. By broadening the scope of the inclusion criteria, gaps from previous studies will be addressed and the resultant analyses - including subgroup analyses - will be more comprehensive, allowing both broader and more nuanced conclusions to be made relating specifically to interventions targeted at improving antepartum and postpartum HIV medication adherence and retention in care.

Currently there is no published systematic review or meta-analysis that incorporates all these elements, with the requisite potential for the a priori subgroup analyses. Findings across these expanded criteria have the potential to assist public health officials and policy makers in evidence-based decision making in research, healthcare and policy development around effective antenatal and postnatal care interventions to improve HIV adherence and retention in maternal populations. It can also shed light on whether antenatal or postnatal care interventions offers the greatest potential for reaching women to improve adherence and retention. This could provide data on where to direct resources to achieve the greatest benefit.

1.3 Research question and Objectives

Main review question: In HIV-infected women on ART, which antenatal and/or postnatal care interventions, preconception or interconception care strategies improve medication adherence and retention in care during pregnancy and/or postpartum?

The primary objectives for the review are to assess and synthesise global evidence regarding interventions before, during and after pregnancy focused on improving ART adherence and/or retention of HIV-infected pregnant and postpartum women during the antenatal and postnatal care periods. This would include women initiating as well as conceiving on ART, to further determine: 1) the types of antenatal and postnatal care interventions, for pregnant and postpartum women respectively, 2) if antenatal interventions improve postpartum adherence and retention outcomes, 3) if preconception and interconception care improves ART adherence and retention during the antenatal and postnatal periods and 3) what duration and types of interventions are most effective in improving ART adherence and retention.

2 METHODOLOGY

The review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24).

2.1 Inclusion and Exclusion Study Criteria

2.1.1 Inclusion Criteria

- All study designs will be considered, including randomised controlled trials, quasi-randomised trails, pre/post studies, retrospective and prospective cohorts, and case control studies using antenatal or postnatal care interventions to improve ART adherence and/or retention in care

- Target population will include HIV-infected women, aged 18 and older, on ART during and after pregnancy. This will include women already on ART or those initiating at an ANC visit. Postpartum is defined as beginning at 6 weeks with no end period and includes breastfeeding women
- All types (e.g. peer mentors, mobile health interventions, etc.) and durations (days, months, years) of antenatal and postnatal care interventions will be considered, including those targeting mothers only, infants only and mother-baby dyads
- Studies published between 1990 to August 2019 will be considered
- All geographical regions will be included
- Studies published in English will be included

2.1.2 Exclusion Criteria

- Mathematical modelling studies, guidelines, study protocols, reviews and case series will not be considered
- HIV-infected adolescents aged 17 and younger
- Much of the literature refers to Option B+ as an intervention. Studies that consider Option B+ as an intervention will be excluded since this review is not focused on ART eligibility, but on what interventions exist for eligible women on ART to improve their adherence and retention in care during and after pregnancy. PCC and ICC targeted at WLHIV, will also be considered as it relates to ART adherence during pregnancy and postpartum
- Studies with participants from high-risk or key populations i.e. prisoners, sex workers, etc.
- Studies published before 1990
- Studies published in languages other than English

2.2 Outcome

The review outcome will explore improvement in ART adherence and retention in care post-intervention. Adherence measures will be categorised as follows: subjective measures (e.g. self-report by patients), objective measures (e.g. pill count, pharmacy refill, and electronic device monitoring), and biological correlates of adherence (e.g. viral load, plasma drug levels (25). Other measures identified from included studies will be categorised into one of these groups. Adherence will be defined as per the study author definition, and may be expressed as percentage of medication taken correctly for a defined study period (e.g. 100% medication taken for 6 months) or viral suppression.

If multiple adherence measures are presented in a paper, one of which is a combined measure (i.e. pooling of 2 or more adherence measures), the single adherence measure outcome/s will only be

reported and analysed (i.e. the combined measure will be excluded). However, in the event a study only reports combined outcomes, the paper will be retained and reported as a combined measure to prevent loss of data by study exclusion.

Retention in care post-intervention will be categorised from the date of initiation of ART according to the relevant study defined criteria of a visit e.g. attending clinic appointments. The type of encounter considered as a visit will also be study defined e.g. doctor appointment, medication pick-up, follow-up contact etc. Retention measures considered will be numbers/proportion: retained in care and lost-to-follow-up (as reported in the study, including those who died, and stopped treatment). Women will be considered retained if reported as transferring care or not following other aspects of care while still attending visits (11). Other measures, and possibly duration of time (e.g. between visits or since the last visit), may later be identified from included studies. If the data allows, the suggested definition of retention of care from a recent systematic review (11), i.e. having attended a clinic appointment within the last 90 days, will be calculated from study data.

2.3 Search strategy for identification of studies

A comprehensive literature search will be performed to enable capturing of as many relevant articles as possible. The following online electronic databases will be searched from 1990 to 2019: the Cochrane Library; MEDLINE via PubMed; Web of Science; Academic Search Premier, Africa Wide, CINAHL, Health Source Nursing Academic, PsychARTICLES via the Ebscohost platform; and Global Index Medicus. Conference abstracts to be searched until 2019 include AIDS, the International AIDS Society (IAS), and the Conference on Retroviruses and Opportunistic Infections (CROI), which will be compared to the search results to ensure that all relevant articles are considered in this review. Reference lists of relevant studies will be searched for further articles. No geographical limitations will be applied. Medical subject headings (MeSH) and text words related to HIV, ART, pregnancy, postpartum, breastfeeding, interventions, treatment adherence and retention, will be used (Table 1). Guidance from the medical librarian at the Health Sciences Library at the University of Cape Town will be sought before the final search processes are performed.

Table 1: Keywords and MeSH Terms to be used in database searches

Search	Query
#1	Search ((HIV [MeSH Terms]) OR HIV Infections [MeSH Terms]) OR ((HIV OR HIV-1 OR HIV-2 OR HIV1 OR HIV2 OR Human Immunodeficiency Virus OR Human Immunedeficiency Virus OR Human Immune-Deficiency Virus OR Human Immuno-Deficiency Virus OR Acquired Immunodeficiency Syndrome OR Acquired Immunedeficiency Syndrome OR Acquired

Search	Query
	Immuno-Deficiency Syndrome OR Acquired Immune-Deficiency Syndrome OR Nevirapine OR Zidovudine))
#2	Search ((Antiviral Agents [MeSH Terms]) OR Antiretroviral Therapy, Highly Active [MeSH Terms]) OR ((anti-AIDS OR anti-HIV OR anti HIV OR antiretroviral OR anti-retroviral OR anti retroviral OR HAART))
#3	Search ((((Pregnancy [MeSH Terms]) OR Pregnant Women[MeSH Terms]) OR Postnatal Care[MeSH Terms]) OR Postpartum Period[MeSH Terms] OR Preconception Care[MeSH Terms]) OR ((pregnant OR antenatal OR interconception OR postnatal OR perinatal OR postpartum OR preconception OR prenatal OR mother-to-child OR MTCT OR mother-to-infant OR maternal-infant transmission OR PMTCT))
#4	Search ((((Treatment Adherence and Compliance [MeSH Terms]))) OR Lost to Follow-Up [MeSH Terms]) OR ((adherence OR engagement OR care acceptor OR compliance OR patient acceptance OR retention OR loss to follow up OR lost to follow-up OR lost to follow up OR linkage to care OR pharmacy refill OR self-report OR electronic device monitoring OR plasma drug levels))
#5	#1 AND #2 AND #3 AND #4

3 DATA COLLECTION AND ANALYSES

3.1 Study selection

All titles and abstracts identified by database searches will be entered into a reference manager (Endnote) and duplicates removed manually. These will be screened in duplicate by two reviewers and articles for full text review identified. The full text review of relevant articles will also be performed in duplicate to determine the final selection of articles for inclusion in the review.

3.2 Data extraction

Data extraction will be performed according to a standardised extraction form in duplicate by two separate reviewers. Discrepancies will be resolved by discussion and consensus with resolution by a third senior reviewer where necessary. A pilot extraction with a draft extraction form will be performed on approximately 10 articles to determine if all relevant information from interventions are being captured. Currently the data to be extracted from each study includes: first author, year, country, rural/urban setting, study design, study duration, populations (mother/infant/both), pregnancy/postpartum, infant age, adherence measure, adherence definition, control group, antenatal/postnatal intervention, type of intervention, duration of intervention, who the intervention was administered by, intervention description, and adherence outcome.

3.3 Assessing risk of bias

Assessment of study quality of included studies will be performed independently in duplicate by two separate reviewers. Discrepancies will be resolved by discussion and consensus with resolution by a third senior reviewer where necessary. Due to varied study designs anticipated, two different tools have been identified to assess risk of bias. For randomised trials the tool recommended by the Cochrane Collaboration (26) will be used, which includes domains related to sequence generation, allocation concealment, masking of participants and outcome assessors, incomplete outcome data, and selective outcome reporting covering a range of potential biases. For non-randomised studies the ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions) tool will be used (27) Domains for this tool include bias due to confounding and participant selection (pre-intervention), bias in classifications of interventions (at intervention), and bias due to deviation from intended interventions, missing data, outcome measurements and selection of reported results (post-intervention).

3.4 Dealing with missing data

It is expected that some published articles may be inaccessible. The University of Cape Town has high access to published journal articles but where embargo periods or journal subscriptions prevent accessing of relevant articles, study authors will be contacted. This will also be done where full data is unclear or missing. A request for the article or data will be sent to the corresponding author, and in the event of a non-response a follow up email will be sent. If the requested information is not sent or the author does not respond after two attempts, the article in question will be excluded from the study.

3.5 Measure of intervention effect

Data will be analysed using Review Manager 5.3 (Cochrane Collaboration, 2008). The likely nature of the adherence outcome will be dichotomous (adherent or non-adherent). It is anticipated that effectiveness of interventions from each study will be expressed as an odds ratio (OR) or risk ratio (RR) with 95% confidence intervals.

3.6 Assessment of heterogeneity

Heterogeneity will be assessed with Cochran's Q statistic and the I^2 statistic (28) I2 values greater than 75% indicate substantial heterogeneity while a low degree of heterogeneity (50% or lower) will indicate a meta-analysis is possible. In the event of homogenous studies, a fixed effects model will be

used to determine pooled effects. Alternatively, a random effects model will be used if interventions are heterogeneous.

3.7 Subgroup analysis

A priori subgroups have been identified for subgroup analysis, and will be conducted if possible from data extracted (it should be noted that in some cases data may be insufficient to allow these analyses). These will include stratifying and analysing studies by: study design; antenatal or postnatal intervention, ICC or PCC; interventions geared towards mothers only, infants only or the mother-infant dyad; intervention type; duration of intervention; type of adherence measure; and duration of postpartum period by breastfeeding or non-breastfeeding mothers. While not a subgroup analysis, the ART eligibility policy at the time of the study will also be considered in the assessment of the results e.g. when women began ART at CD4 count of <350 when compared to Option B+.

3.8 Presenting and reporting of results

A descriptive narrative approach will be adopted for results reporting if there is substantial heterogeneity in included studies. Results will be presented using a combination of tables, figures and/or graphs where appropriate. Forest plots will be used to assess heterogeneity of included studies, and where the latter is high summary tables will be generated to summarise data. Chi-squared tests will be conducted to assess between study homogeneity. Funnel plots assessing publication bias will also be reported. Excluded studies will be tabulated, together with justification for exclusion.

The second, validated Pragmatic–Explanatory Continuum Indicator Summary (PRECIS-2) (29) tool will be used to evaluate whether identified interventions are pragmatic or exploratory. This will aid assessment of intervention performance in real world settings. The tool consisting of 9 domains (eligibility criteria, recruitment, setting, organisation, flexibility regarding delivery), flexibility regarding adherence, follow-up, primary outcome, and primary analysis) will be reported either diagrammatically or tabulated depending on our results.

4 ETHICS

Given that this is a systematic review of publicly available, published data, there will be no direct engagement with human subjects. Ethical approval is thus not required and will be not be sought.

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PART B: MANUSCRIPT

Interventions for Improving Adherence and Retention in HIV-Infected Women on ART During Antenatal and Postnatal Care: A Systematic Review

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Abstract

Background Universal access to antiretroviral therapy during pregnancy and breastfeeding has implications for retention in HIV care and adherence to antiretroviral therapy (ART). Retention and adherence may be especially challenging during antenatal and postnatal care, where women living with HIV have competing responsibilities between infant care, self-care and personal responsibilities. Lifelong ART also highlights the role interconception and preconception care interventions can play in improving maternal outcomes. This systematic review evaluates interventions that aim to improve retention and adherence in pregnant and postpartum women.

Methods We searched Pubmed, Scopus, Web of Science, Cochrane Library, EBSCOhost and conference databases for articles in English published between 1990 to 2020. All study designs, intervention types and geographic locations were included. Data was extracted using a standard tool, and effect sizes recalculated for all studies. Risk of bias was conducted using tools suited to specific study designs, and the PRECIS-2 tool assessed intervention applicability in real-world settings.

Results Thirty-one studies were identified, of which 31 and 16 provided retention and adherence data respectively. No interconception or preconception care interventions were found. Interventions were predominantly from Sub-Saharan Africa, except one from the USA. Intervention types varied and included integration of services, peer support, mhealth and multicomponent interventions. The definitions of retention and adherence used for outcome assessment varied widely across studies, but almost all were scored as pragmatic in real-world settings. Due to high heterogeneity, a narrative approach was used based on study reported data and the effect sizes.

Conclusion Overall, heterogeneity of identified studies make definitive recommendations for interventions scale up difficult. Future intervention evaluation will benefit from consistent study designs, outcome definitions, outcome measurements, validated tools, and longer retention time points will strengthen the evidence base. Ongoing studies being conducted show promise in addressing some of these points.

Keywords: HIV, antiretroviral therapy, adherence, retention, interconception care, preconception care, antenatal, postnatal, pregnant, postpartum

1 INTRODUCTION

In recent years global prevention of mother to child HIV transmission (PMTCT) policies have shifted to focus on universal, lifelong antiretroviral therapy (ART) for all pregnant and breastfeeding women [1]. While beneficial to ensure reduced vertical HIV transmission to infants and improved maternal outcomes, this approach relies on sustained retention in care and adherence to ART [2]. Suboptimal retention and adherence leads to poor outcomes including ART resistance, virologic rebound, uncontrolled viraemia, disease progression and increased risk of vertical transmission to the infant if the mother is breastfeeding [2-4].

Data from a recent systematic review showed that pregnant and postpartum women in Africa have low retention rates of 79.4% and 74.5%, 6 and 12 months respectively, post-ART initiation [5]. Another review showed pooled estimates for adequate adherence (≥80%) were low antenatally and even more postnatally, at 73.5% and 53% respectively [6]. There are several reasons for suboptimal maternal care during pregnancy and postpartum. These include: pill fatigue [6]; ART side effects [7, 8]; forgetting to take medication[9, 10] lack of partner or family support [6, 7]; perception that care is not needed [9, 11]; time commitments [9, 11]; transportation logistics and costs[11]; poor health care workers (HCWs) attitudes [7, 11, 12]; stigma [13, 14]; lack of HCW confidentiality [15]; clinic distance [7, 8] and patient readiness for ART initiation. Other unique barriers exist, such as pregnancy associated nausea and heartburn which can be worsened by ART [6]. Women diagnosed positive and initiating ART during pregnancy can also be overwhelmed by the trifecta of reconciling with their diagnosis, adjusting to being pregnant, and the prospect of facing an ART regimen daily, for life (9). Postpartum, women have to balance recovering from childbirth, breastfeeding, emotional stressors associated with caring for a new born and potentially, postpartum depression [2, 6, 7, 16]. During the antenatal period, maternal motivation for remaining in care is tied to protecting the unborn infants health, but post-delivery mothers consider their own treatment less important [17]. Additionally, after birth women are faced with a move from concurrent maternal and in utero infant care to separate care post-delivery [11, 18], a significant demotivator to retention and adherence [2], while facing challenges of caring for a new infant [7]. Some mothers who have not disclosed their HIV status to family, feel they no longer have an acceptable reason for clinic attendance post-delivery [18]. These scenarios

account for higher retention and adherence levels seen in antenatal care (ANC) compared to postnatal care (PNC), highlighting the critical need for implementation of effective, evidence based interventions to enhance retention and adherence during these periods.

Previous systematic reviews of interventions to improve retention found mixed results [19] and a weak evidence base of interventions targeted at improving retention in postpartum women although phone based interventions showed efficacy at 3 months postnatally [20]. However, this is still very early in the postpartum period. Poor retention across various ART regimens point to the need for effective interventions rather than simpler regimens to address HIV care retention [21].

In addition to ANC and PNC interventions, preconception and interconception care (PCC and ICC, respectively) can address maternal health over broader periods outside of pregnancy and postpartum. PCC and ICC are defined as sets of interventions directed at women and/or couples of childbearing age, regardless of pregnancy status or desire, pre-pregnancy or between pregnancies, to improve health outcomes for women, newborns and children (22). While PCC and ICC interventions have been explored for maternal substance use, nutrition, diabetes and obesity to improve parental behaviours and outcomes [22], those in the field of HIV are lacking. PCC and ICC for HIV-infected individuals are more focused taking the form of promotion of safer conception between serodiscordant couples, planned pregnancies, and prevention of HIV vertical transmission between the mother and infant [23]. PCC and ICC directed at women living with HIV (WLHIV) thus has the potential to influence retention and ART adherence before, during and after pregnancy.

The challenges, consequences and implications described above underscore the critical need for effective interventions to retain pregnant and postpartum women in care and keep them adherent to ART. This systematic review aims to: 1) identify all interventions that address adherence to ART and retention in care for pregnant and postpartum women as well as those in ICC or PCC stages; 2) determine which interventions successfully improve these outcomes; and 3) assess the real world applicability of these interventions.

2 METHODS

2.1 Search strategy

The following online electronic databases were searched from January 1, 1990 to January 7, 2020: the Cochrane Library; MEDLINE via PubMed; Web of Science; and EBSCOHOST (Africa Wide, Academic Search Premier, CINAHL, PsychArticles, Health Source Nursing Academic, PsychInfo). Conference abstracts searched non-exhaustively until December 2019 included AIDS, the International AIDS Society, and the Conference on Retroviruses and Opportunistic Infections. Secondary references were obtained from searching reference lists of relevant studies and reviews. No geographical or language restrictions were applied. Medical subject headings (MeSH) and text words related to HIV, ART, pregnancy, postpartum, breastfeeding, interventions, treatment adherence and retention were used (S1 Table). The protocol was registered with PROSPERO (ID: CRD42020185196).

2.2 Inclusion and exclusion criteria

Studies were included if they: (a) were in English, (b) were published after 1990, (c) included pregnant or postpartum women living with HIV as the target population (either on or newly initiated on ART), (d) evaluated an intervention with a primary or secondary outcome of retention in care or adherence to ART; (e) had study designs with or without a control or comparison group, and (f) were from any geographic region. Studies with HIV uninfected pregnant or postpartum women, that referred to therapeutic ART regimens as an intervention, or with high risk populations, were excluded. Studies focusing on infants as the study population were considered only if they reported maternal outcomes separately or reported data for mother-infant pairs (MIPs). Studies reporting only infant outcomes were excluded. Dissertations, reviews, case reports, studies reporting no quantitative data, and qualitative studies were excluded. Relevant abstracts and ongoing studies without results were excluded but compiled into a non-exhaustive list and reported separately.

Study populations were categorised as: pregnant, if women were recruited and evaluated in pregnancy only; postpartum, if the intervention recruited and followed up women or MIPs during the postpartum period; and pregnant/postpartum if they were recruited during pregnancy and followed up after delivery (included MIPs).

2.3 Data extraction

One reviewer screened search results and extracted data independently, with issues resolved through discussion with a second reviewer. Using a standardised extraction template, data was extracted regarding: author, publication year, country, study design, period of data collection, length of follow up, study population, intervention type and description, control description, sample size, outcome measure(s) and definitions, and study results.

2.4 Risk of Bias

Risk of bias (ROB) was assessed using 3 tools from the COCHRANE collaboration. For randomised controlled trials (RCTs) the ROB-2 (updated in 2019) for individually randomised trials [24], and a similar version of this tool with additional questions specific to cluster-randomised controlled trials (cRCTs)[25] was used to assess respective study designs. Studies were categorised as being either critical, high, some concerns or low risk of bias. Non-randomised trials were assessed using ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions) [26]. ROB was assessed for each overall outcome for studies reporting more than one outcome. All ROB figures were generated using the robvis online tool [27]. One reviewer assessed ROB with uncertainties resolved through discussion with the second reviewer.

2.5 Data analysis

Apart from extractions of author reported risk ratios (RRs) or odds ratios (ORs), effects sizes were recalculated as ORs with 95% confidence intervals (CIs) for each outcome. Analysis was conducted on subgroups by outcome, study population, intervention type and outcomes measures. The large degree of heterogeneity generated from preliminary analysis of results meant a descriptive narrative approach would be adopted with measures of associations reported per subgroup [28]. Review manager 5.3 was used to generate analysis forest plots for subgroups.

The validated Pragmatic–Explanatory Continuum Indicator Summary (PRECIS-2) tool was used to evaluate if interventions were very pragmatic or rather pragmatic (score of 5 or 4), equally pragmatic/exploratory (score of 3), or very or rather explanatory (score or 1 or 2) to indicate intervention performance in real world settings[29]. Each included study was assessed across

the 9 domains - eligibility criteria, recruitment, setting, organisation, flexibility regarding delivery, flexibility regarding adherence, follow-up, primary outcome, and primary analysis. Average PRECIS-2 scores and standard deviations were calculated for each study and domain by intervention and outcome. This assessment was completed by one reviewer with issues resolved through discussion with a second reviewer.

3 RESULTS

3.1 Search Results

Database results retrieved 6082 records with an additional 17 identified through reference lists of included articles and relevant reviews (Fig 1). After removing duplicates, screening abstracts, and full-text review of 126 articles, 33 [30-62] studies met the full inclusion criteria. In total 93 studies were excluded (S2 Table). No studies explored interventions implemented in ICC or PCC periods.

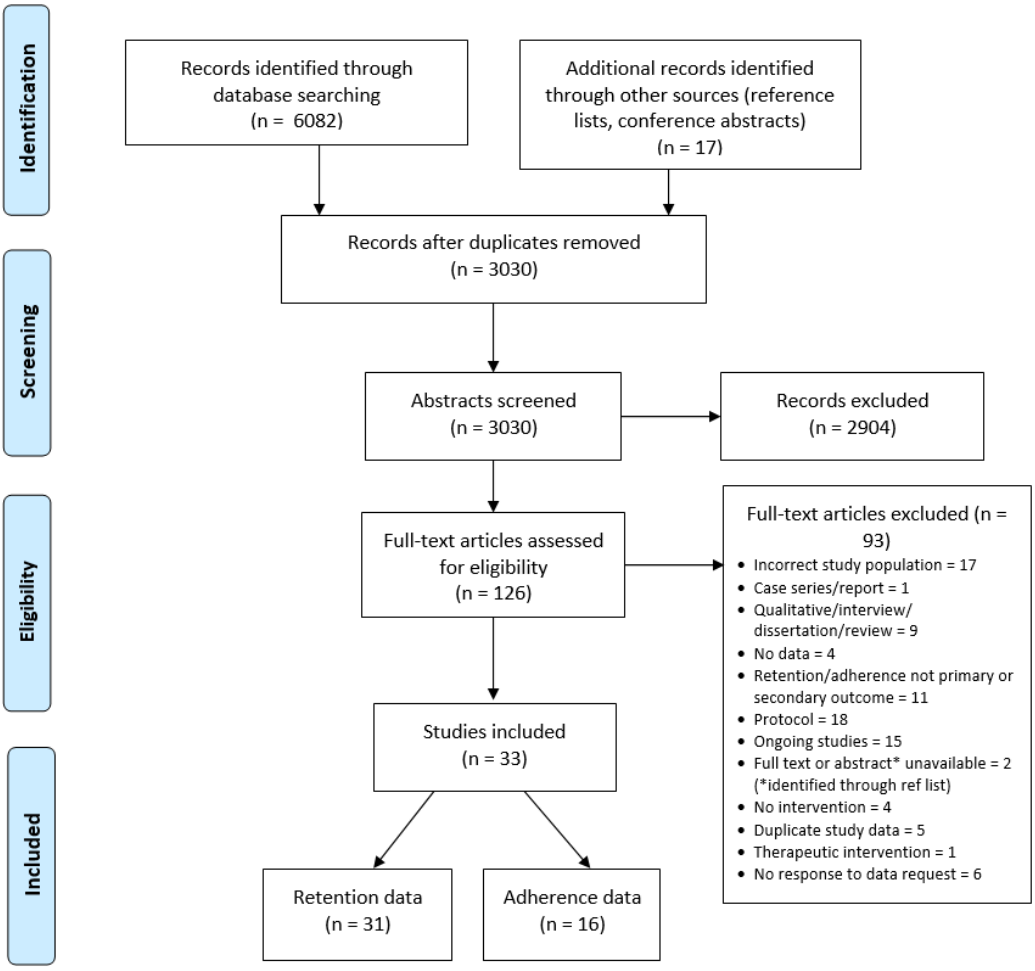
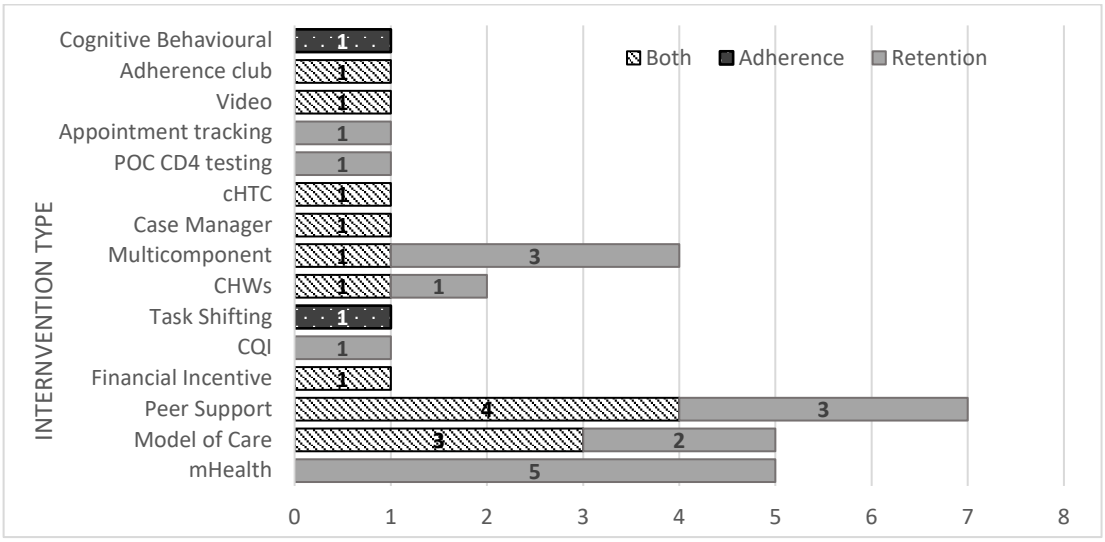


Figure 1: PRISMA flow diagram of the systematic review search process.

3.2 Characteristics of included studies

Sixteen and 31 articles provided data on adherence and retention, respectively. Many studies assessed both outcomes in both pregnant and postpartum women (Fig 2a). Intervention types were categorised as far as possible into broad groups: mHealth, including text messages and phone calls; model of care, which was composed of service delivery models and integrated care models; peer support which was composed of mentor mothers, expert mothers and any type of peer related support; financial incentives; quality improvement (QI); task shifting; cognitive behavioural risk reduction and multicomponent interventions. The latter was labelled as such since most studies in this group combined multiple interventions from the former groups. Characteristics of included studies by intervention type, location and study design are given in Figs 2a., 2b. and 2c. respectively.



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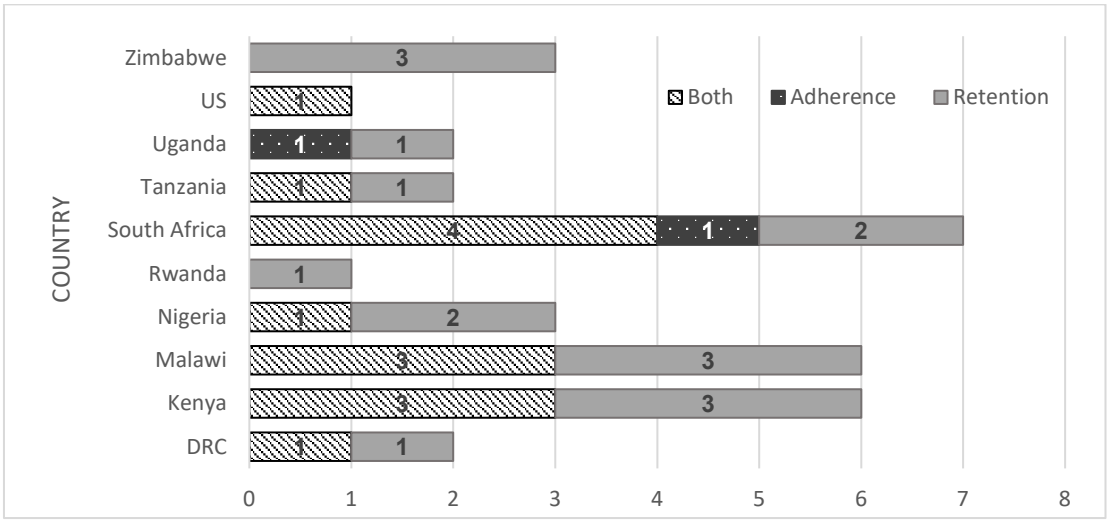

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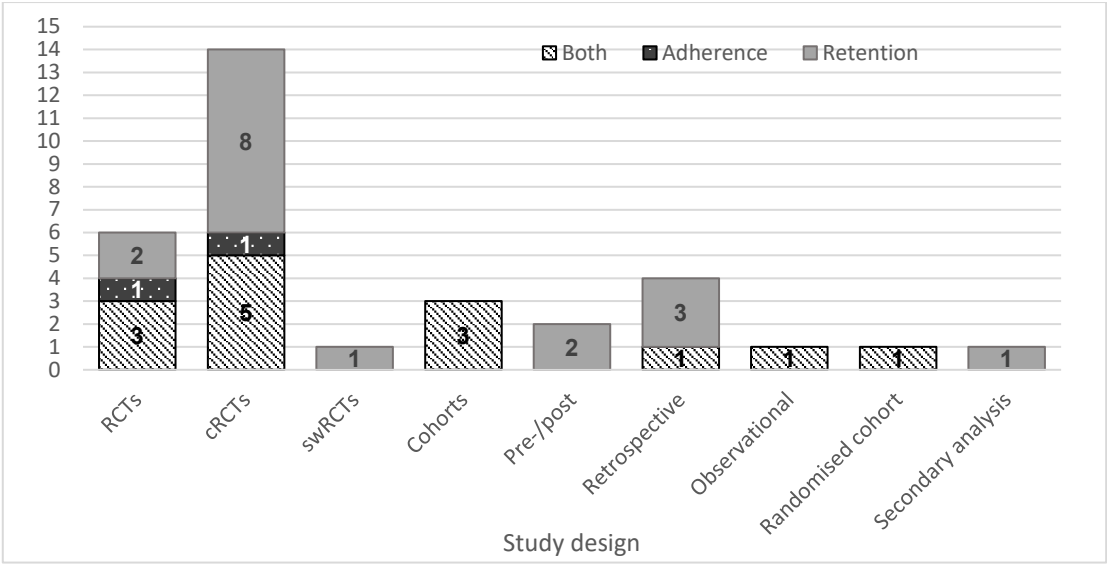


Figure 2: Study characteristics of included studies by outcome are described by: 2a) intervention type 2b) location and 2c) study design. Both refer to studies investigating both adherence and retention outcomes.

3.3 Retention

Descriptions of interventions focussing on retention are given in Table 1. Individual study sample sizes ranged from 71 to 3150.Pooled sample sizes from all studies included 671 pregnant women (n=3) and 6239 postpartum women (n=5). The remaining studies (n=23) that recruited women during pregnancy and followed them through to postpartum has pooled sample sizes of 15611 women.

Maternal retention was measured at varied, multiple time points across studies from short term (ranging from the second ANC visit and delivery to 14 weeks postpartum) to longer term retention (ranging from 6 months to 24 months postpartum).

Table 1: Characteristics of included studies for retention in pregnant and postpartum women (n= 31), ordered alphabetically by intervention type and author

AUTHOR, YEAR	COUNTRY	STUDY DESIGN	PERIOD OF DATA COLLECTION	RETENTION ASSESSMENT TIME POINTS	RECRUITED AT TIMEPOINT/ LOCATION	POPULATION	INTERVENTION DESCRIPTION	CONTROL DESCRIPTION
ADHERENCE CLUBS								
Myer, 2017	South Africa	cohort	February to September 2015	6 months postpartum	routine postpartum visit	postpartum	Community-based adherence clubs separate from health facilities aided by lay counsellors, symptom review and HIV/health-related group educational talks at each 2 to 4 monthly visit (average 5 per year per club). Prepacked ART dispensed, patients permitted proxies to collect medication. Within club system clinical review annually with nurse evaluation and VL testing	Referral to local PHC
APPOINTMENT TRACKING								
Ross-Degnan, 2017	Tanzania	cRCT	April 2015 to April 2016	6 months	RCH clinics	postpartum	Paper based appointment tracking and community outreach consisting of training, supportive supervision, and early community-based follow-up to encourage return to care using standardized paper-based appointment register, another register to track patients missing appointments; and monitoring monthly proportion of patients attending appointments on time.	MOHSW's previous distribution of appointment and patient-tracking registers
CASE MANAGERS								
Anderson, 2017	USA	retrospective	2005 to 2013	≤90 days post-delivery, 12m	Not mentioned	pregnant, postpartum, MIPS	Perinatal Medical Case Management Program: case workers worked with WLWH during pregnancy until 1 year postpartum providing psychosocial support, addressing structural, psychosocial and other barriers to medical care, and identifying unmet needs.	Women with HIV not in PCM
COMMUNITY HEALTH WORKERS								
Nance, 2017	Tanzania	cRCT	May 2015 to March 2016	60 -120 days postpartum	unclear, probably pregnancy	pregnant, postpartum	CHW-led ART adherence counselling; defaulter tracing, distribution of Action Birth Cards a birth planning tool as an ANC visit reminder. CHW helped women plan for delivery, and encouraged HIV+ women to receive care	No CHW led intervention
Vogt, 2015	Zimbabwe	retrospective	February 2010 to March 2013	delivery	during ANC	pregnant, postpartum	CHW based defaulter tracing by mobile phone, or if no number/unsuccessful call, home visit. Tracing letters left if no personal contact could be made. Returning defaulters received minimum one counselling session.	None
COUPLES HIV COUNSELLING AND TESTING								
Wesevich, 2017	Malawi	observational	March to September 2014	1 month post ART initiation	first ANC visit	pregnant	Paper invitations only versus paper invitations plus phone and physical partner tracing, encouraging men to attend ANC with female partners for health information.	No cHTC
FINANCIAL INCENTIVE								
Yotebieng, 2016	DRC	RCT	April 2013 to August 2014	6 weeks postpartum	<32 weeks gestation registered for ANC	pregnant, postpartum	SOC and US$5, plus US$1 increase at every subsequent visit if woman attended scheduled visits, provided blood sample for CD4 count on request, accepted ART referral, delivered in a health facility, provided blood sample for infant early HIV diagnosis at 6 weeks postpartum	SOC
MHEALTH								
Coleman, 2017	South Africa	retrospective	April 2013 to August 2014	messages sent until infant 6 weeks PCR test	1st or 2nd ANC visit	pregnant, postpartum	Unidirectional, twice weekly MAMA SMSs offered to ANC patients providing maternal health information during pregnancy and 1 year after birth. Messages timed to gestational/infant age and covered maternal health and HIV-support	No SMS
Odeny, 2014	Kenya	RCT	April 2012 to March 2013	8 weeks postpartum	attending ANC, between 28 weeks and delivery	pregnant, postpartum	14 text messages (eight during pregnancy, six postpartum), weekly calls from 38 weeks' gestation until delivery. Participants in both arms were allowed to call or send SMS to the study nurse at any time.	SOC contact by phone / in person if visit missed.
Odeny, 2019	Kenya	swcRCT	February 2015 to	8 weeks after delivery	attending PMTCT, between 28 weeks and delivery	pregnant, postpartum	Texting Improves Testing (TextIT), 14 text messages during pregnancy and after delivery, option to respond to text messages, call, or send inquiry text messages to a designated clinic phone.	No TextIT

			December 2016					
Sarna, 2019	Kenya	RCT	May 2013 to September 2015	14 weeks postpartum	14 - 36 weeks gestation	pregnant, postpartum	SOC + Healthy Mother Healthy Baby Project: individualised counseling support via phone. Call number varied depending on presentation for ANC services (max 42). Sessions consisted of 2 calls in first week of starting PMTCT services, then 1 call/week until delivery (max 26 calls), followed by 2 calls during the first week after delivery and 1 call/week for next 14 weeks (max of 16 calls)	Routine HIV counselling from ART clinic-based counsellors
Schwartz, 2015	South Africa	pre/post	May to July 2013	6 weeks, 12 months postpartum	≥36 weeks gestation attending ANC	pregnant, postpartum	Weekly text messages and 1 pre-delivery and 2 post-delivery calls from a case manager until 6 weeks postpartum (or 8 weeks if participant did not return for 6wk clinic visit) to encourage remaining in care and give support.	No text
MODEL OF CARE								
Mwapasa, 2017	Malawi	cRCT	May 2013 to August 2016	12months postpartum	pregnancy	pregnant, postpartum	Promoting Retention among Infants and Mothers Effectively (PRIME): **1. MIP ARM**: integrated MIP clinics with HIV, maternal and child health services at a one time and access point, offered 2x per week monthly. **2. MIP + SMS**: Services provided at one time and access point with use of SMS to notify community based volunteers to trace mother/infant defaulter	SOC provided at multiple times and access points (Usual non-integrated care and patient tracing)
Myer, 2018	South Africa	RCT	January to September 2010	12 months postpartum	<6weeks postpartum during routing follow-up visits	postpartum	Local SOC involves integrated Maternal and Child Health (MCH) and ART services during pregnancy, following the local SOC. Intervention continued this postpartum where women/infants in the MCH clinic received integrated maternal ART and paediatric care until end of breastfeeding or a max 1 year	Transfer from MCH clinic after 1st/2nd postpartum visit to general ART services, infants to separate routine child health services
Turan, 2015	Kenya	cRCT	June 2009 to March 2011	within 6 months of enrollment in care	ANC	pregnant, postpartum	Integrated care at ANC and HIV care and treatment in the same clinic until 18 m post-partum	SOC (ANC referral for HIV care and treatment at same facility but different clinic)
Washington, 2015	Kenya	cRCT	June 2009 to March 2011	12 months after enrolment	during pregnancy	pregnant, postpartum	Combined ANC, PMTCT, and HIV care and treatment in the same clinic. Same clinician provided ANC and postpartum services including EID until a definitive paediatric HIV diagnosis was obtained or infant 18m old. MIP, if HIV infected, then referred to long-term care at facility's HIV clinic.	routine ANC and PMTCT services as per national Guidelines.
Weigel, 2012	Malawi	pre/post	July 2006 to October 2010	6 months after ART initiation	first ANC visit	pregnant, postpartum	3 year model of care involving paper based tracking system, vehicles for transport between ANC and ART facilities, establishment of a new HIV care centre near the ANC clinic, priority of PMTCT patients, no need for guardians for ART initiatiation, information leaflets for HIV-positive pregnant women, and an electronic data system for patient care	NA
MULTICOMPONENT INTERVENTIONS								
Aliyu, 2016	Nigeria	cRCT	April 2013 to March 2014	6 and 12 weeks postpartum	recruited during ANC or delivery	pregnant women or MIPS	Task shifting from doctors to nurses/ midwives/CHWs, POC CD4 testing, integrated mother and infant care, family/ male partner participation (written invitations to male partners to attend PMTCT) and community engagement	SOC referred women to nearby secondary level clinic
Fayorsey, 2019	Kenya	RCT	September 2013 to 2015	6 months postpartum	initiating ANC	pregnant, postpartum	Lay counsellors provided individualized PMTCT health education, defaulter tracing; retention/adherence support; phone/SMS visit reminders; expedited service provision, enhancied communication between women and providers, problem-solving retention and adherence barriers, providing psychosocial support and counselling	Routine care per national guidelines, phone follow-up for missed visits, home visit if call unsuccessful
Gill, 2017	DRC	cRCT	May to October 2015	2nd ANC visit	first ANC visit	pregnant	Elombe Standard Operating Procedure (SOP), outlined referral to mentor mothers; topics for first counselling visit; counselling sessions, support group attendance and nutrition; text/call reminders for second ANC visit; call on day of missed visit; home visit	SOC Mentor Mother included counseling at ANC and defaulter tracing
Guillaine, 2017	Rwanda	retrospective	July 2012 to June 2013	18 months postpartum	Not mentioned	postpartum, MIPS	Combined Clinic model: MIP services delivered at single point of care until infant 18 months, mothers enrolled in the community based program, received daily home visits from lay CHWs, nutritional supplementation, monthly	None

							provision of artificial milk formula and equipment, porridge and sugar. Monthly alerts from electronic medical record system to clinicians for delayed patient visits and clinically significant events	
PEER SUPPORT								
Foster 2017	Zimbabwe	cRCT	July 2014 to October 2015	12m postpartum	ANC 35 weeks gestation	pregnant, postpartum	EPAZ (Eliminating Paediatric AIDS in Zimbabwe). "Expert Mothers" coordinated facility-based mother support groups, 2x per month by HCWs until 6 months postpartum. HCWs and group coordinators aided structured learning activities about 8 PMTCT topics over each 4-month cycle. Women received psychosocial support from other women during meetings	Routine PMTCT services only
Futterman 2010	South Africa	cohort	2006 to 2007	6 months post delivery	HIV+ pregnant attending medical obstetric unit	pregnant, postpartum	Mamekhaya: mentoring mothers delivered 8 sessions of a cognitive-behavioural intervention focused on prevention of HIV transmission, adherence to pre- and post-natal baby treatment, uptake of EID	Control site received SOC from midwives and counsellors
Hosseinipour , 2017	Malawi	cRCT	Not Specified	6 months	enrolled at HIV diagnosis in ANC/ postpartum clinic	pregnant, postpartum	Facility-based Peer Support and Community based Peer support	SOC
Igumbor 2019	Uganda	cohort (secondary analysis)	January 2011 to March 2014	6 weeks post-delivery, 6 weeks post-cessation of BF, 18m postpartum	HIV+ attending PMTCT during study period	postpartum, MIPS	SOC + psychosocial support provided by the Mentor Mothers from m2m.	SOC as per Ugandan guidelines,
Phiri, 2017	Malawi	cRCT	November 2013 to July 2016	2 year post ART initiation at 12m and 24m	ANC, maternity, PNC and ART clinics (pregnant and BB women)	pregnant, postpartum	**Facility based peer support:** SOC, "mentor mothers" gave one-on-one support at visits, led weekly clinic-based support groups, contacted women within 1 week of a missed appointment (by phone call/text message/home visit). C**ommunity-based peer suppor**t, received SOC and "expert mothers" conducted routine home visits, HIV education, clinic visit reminders, led monthly community-based support group meetings, contacted women in community within 1 week of a missed visit and 1 home visit reminder for scheduled visit	SOC, routine HIV care per MOH, defaulter tracing for women not attending the clinic within 60 days of a missed appointment
Richter, 2014	South Africa	cRCT	July 2008 to April 2010	1.5 months post birth	during pregnancy at CHC or PHC	pregnant, postpartum	Masihambisane offered Peer Mentor support to pregnant WLH in PHC clinic programs, consisting of 4 ANC and 4 PNC small group sessions in addition to SOC	SOC, based on national guidelines to prevent mother-to-child transmission
Sam-Agudu, 2017	Nigeria	cohort	April 2014 to September 2016	6 months postpartum	unclear, had to have attended at least 1 ANC visit before delivery	pregnant, postpartum, MIPS	Structured Mother Mentor (MoMent), comprised an outcome-specific scope of work, close mentor mother supervision, standardized documentation, performance evaluations	SOC routine informal, non-structured peer support
POC CD4 TESTING AND CD4 COUNT–SPECIFIC ADHERENCE COUNSELING								
Joseph, 2017	Zimbabwe	cRCT	January 2014 to June 2015	6 and 12 months	attending their ANC booking	pregnant, postpartum	POC Plus (POC CD4 testing with CD4 count–specific adherence counseling)	SOC (laboratory-based CD4 testing)
QUALITY IMPROVEMENT								
Oyeledun, 2017	Nigeria	cRCT	March 2014 to October 2016	6 months postpartum	first ANC booking ≤34 weeks	pregnant, postpartum	QI teams composed of facility head/medical officer, study nurses/ CHWs, and laboratory technicians discussed areas for improvement, tracked changes in performance of implemented ideas, adopted/dropped changes based on trends.	Routine Nigerian MOH support
VIDEO								
Kim, 2019	Malawi	randomised pilot	December 2016 and February 2018	1 month	presenting for ANC	pregnant	VITAL Start (Video-intervention to Inspire Treatment Adherence for Life) viewing before committing to lifelong ART. Comprised of information, motivation and behavioural components, with a video of 27 minutes and a post video counselling content of 8 minutes each.	SOC made up of HCW delivered counselling session consisting of all key concepts in the video

Table 2: Results and effect sizes extracted from included retention studies (n=31) in pregnant and postpartum women by intervention.

AUTHOR, YEAR	POPULATION	RETENTION OUTCOME MEASURE TIMEPOINT	Intervention n/N (%)	Control n/N (%)	Effect size (95% CI), p-value	ROB
ADHERENCE CLUBS						
Myer, 2017	Postpartum women	Remained in study	77/84 (91.6%)	34/45 (75.5%)	Not reported	Serious€
APPOINTMENT TRACKING						
Ross-Degnan, 2017	postpartum	One or more visits in last 3 months	1604/1924 (83.4%)	1065/1226 (86.9%)	13.7% net decrease [-15.4,-12.1], **p < 0.05**	Some concerns§
CASE MANAGERS						
Anderson, 2017	HIV+ postpartum women and HIV exposed infants	retained 1 year postpartum	236/448 (52.7%)	137/401 (34.2%),	OR = 2.06 95%CI 1.56-2.71, **p <0.0001** aOR =1.59 95%CI 1.17- 2.16, **p = 0.0029**	Serious€
COMMUNITY HEALTH WORKERS						
Nance, 2017	HIV+ pregnant and postpartum	retention between 60 - 120 days postpartum	138/304 (45.4%) [d]	164/374 (43.9%) [d]	Not reported	High§
Vogt, 2015	HIV+ pregnant women	retention at delivery	post CHW-DT: 496/579 (85.7%)	pre CHW-DT: 850/1008 (84.3%)	RR 1.02 95% CI 0.97 - 1.06, p =0.470 aRR 1.01 95% CI 0.96 -1.06, p =0.730	Serious€
COUPLES HIV TESTING AND COUNSELLING						
Wesevich, 2017	HIV+ pregnant women	retention within 31 days	110/126 (87.3%)	48/74 (64.9%)	RR 1.35, 95% CI 1.12 - 1.61 (p=0.001) aRR 1.33, 95% CI 1.12 - 1.59 (p=0.001)	Moderate€
QUALITY IMPROVEMENT						
Oyeledun, 2017	HIV+ pregnant women first ANC booking ≤34 weeks, ART naïve	Retention in care at 6 months postpartum	117/264 (44.3%)	102/247 (41.3%)	aRR: 1.08 95% CI 0.78 to 1.48, p=0.902	Some concerns §
		within 90 days before 6 months postpartum visit	196/264 (74.2%)	169/247 (68.4%)	Effect not reported, p= 0.288	
FINANCIAL INCENTIVE						
Yotebieng, 2016	newly diagnosed HIV+, at ≤32 weeks gestational age	Retention at 6 weeks postpartum	174/216 (80.6%)	158/217 (72.8%)	RR 1.11 95% CI 1.00 to 1.24, p=0.0548 aRR 1.13 95% CI 1.02 to 1.26, **p=0.0243**	Some concerns§
MHEALTH						
Coleman, 2017	HIV+ pregnant women at first/2nd ANC visit	At least 4 ANC visits	60/73(82.2%)	55/94 (58,5%)	RR 1.4 95% CI 1.15–1.72, **p = 0.001**	Serious€
Odeny, 2014	HIV+ pregnant women > 28 weeks gestation	attended postpartum visit ≤ 8 weeks post-delivery	8/194 (19.6%)	22/187 (11.8%)	RR 1.66 95% CI 1.02 to 2.70, **p = 0.04**	Some concerns¥
Odeny, 2019	HIV+ pregnant women >28 weeks gestation	retention during first 8 weeks post-delivery	1,548/1,725 (90%)	571 /747 (76%)	RR 1.18 95% CI 1.03–1.34, **p = 0.01** aRR 1.12 95% CI 0.97-1.30, **p=0.1**	Some concerns§
Sarna, 2019	14 HIV treatment clinics, HIV+ pregnant women 14 - 36 weeks gestation	retained at delivery	197/207 (95.2%)	153/197 (77.7%)	Ref, p<0,001	Some concerns¥
		retained at 6 weeks pp	183/195 (93.9%)	137/188 (72.9%)	HR 0.21 95% CI 0.10, 0.43, **p <0.001**	
		retained at 14 weeks pp	160/192 (83.3%)	125/188 (66,5)	HR 0.76 95% CI 0.49, 1.13, p=0.18	
Schwartz, 2015	Recruited HIV+ pregnant 36 weeks gestation	ART retention at 12m post-delivery[a]	39/50 (78%)[a]	38/50 (76%)[a]	Not reported, p=0.71	Serious€
		Actively engaged in HIV care at 10 weeks or transferred to another site	47/50 (94%)	48/50 (96%)	Not reported, p = 0.65	
MODEL OF CARE						
Mwapasa, 2017	HIV+ pregnant, HIV-exposed infants	12m maternal postpartum retention MIP	89/461 (19.3%)	90/396 (22.7%)	aRR 0.85 95% CI 0.56 to 1.30, p = 0.46	high§
		12m Maternal retention MIP+SMS	115/493 (23.3%)		aRR 1.08 95% CI 0.87 to 1.35, p = 0.50	
Myer, 2018	HIV+ postpartum	engagement in HIV care at 12m postpartum	188/233 (81%)	168/238 (71%)	Not reported, **p = 0.013**	low¥

Turan, 2015	HIV+ pregnant	≥ 2 HIV care visits in first 6 months after testing HIV+ in ANC	190/393 (48%)	123/218 (56%)	OR 0.73 95% CI 0.47 to 1.14, not significant [c]	Some concerns§
Washington, 2015	HIV+ pregnant	Retention 12 months	422/569 (74%)	403/603 (66.8%)	Not reported	Some concerns§
Weigel, 2012	HIV+ pregnant, CD4<250, not on ART at 1stANC visit	retention 6 months post-ART initiation	2009: 87/133 (65%)	2006: 9/53 (17%)	Not reported, **p <0.001**	Critical€
MULTICOMPONENT INTERVENTIONS						
Aliyu, 2016	HIV+ pregnant women on ART presenting for ANC or delivery	MIP retention 6 weeks postpartum	125/150 pairs (83%)	15/170 pairs (9%)	RR = 9.4 95% CI 5.5 to 16.1, **p < 0.0001** aRR = 9.1 95% CI 5.2–15.9, **p = 0.002**	Some concerns §
		MIP retention 12 weeks postpartum	112/150 pairs (75%)	11/168 pairs (7%)	RR = 11.4 95% CI 6.1 - 21.2, **p < 0.0001** aRR = 10.3 95% CI 5.4 to 19.7, **p < 0.0001**	
Fayorsey, 2019	HIV+ pregnant women starting ANC	Retained at 6 months postpartum [a]	138/170 (81.2%)[a]	122/170 (71.8%)[a]	Not reported	Low¥
Gill, 2017	HIV+ pregnant women attending first ANC visit	Attended 2nd ANC visit	66/75 (88%)	63/90 (70%)	RR = 2.5 95%CI 1.05–5.98, **p < 0.002**	High§
Guillaine, 2017	HIV+ pregnant mothers and infants	Retained at 18 months [a]	184/185 (99.5%) [a]	NA	None	Serious€
PEER SUPPORT						
Foster, 2017	HIV+, ≤ 35 weeks gestation and HIV exposed infants	point attendance at 12m PNC follow-up	134/188 (71)	98/160 (61)	OR 1.46 95% CI 0.92 - 2.30, p = 0.11	High§
		regular attendance over 12m PNC follow-up	146/188 (78)	113/160 (71)	OR 1.37 95% CI 0.84 to 2.25, p = 0.21	
Futterman, 2010	HIV+ pregnant women	Attended FU	23/40 (57.5%)	11/31 (35.5%)	RR 1.62 95% CI 0.94 - 2.79, p = 0.097	Serious€
Hosseinipour, 2017	HIV+ pregnant and BF women	6 month retention	FBPS 323/428 (75%)	312/447 (70%)	OR 0.81 95% CI 0.45 - 1.40, none reported	High§
			CBPS 315/394 (80%)		OR 1.13 95%CI 0.61 - 2.12, none reported	
Igumbor, 2019	HIV+ pregnant, MIP	retention 6 weeks after birth	1123/1161 (96.7%)	752/1143 (65.8%)	aOR 12.23 95% CI 5.51 - 27.14, **p < 0.05**	Serious€
		retention 6 weeks after cessation of breastfeeding	946/1161 (81.5%)	480/1143 (42.0%)	aOR 4.93 95% CI 2.98 - 8.12, **p < 0.05**	
		retention 18m after birth	826/1161 (71.2%)	235/1143 (20.6%)	aOR 8.65 95% CI 4.80 -15.59, **p < 0.05**	
Phiri, 2017	HIV+ pregnant	Maternal retention 12m [a]	FBPS: 287/366 (78.4%)[a]	270/361 (74.8%)[a]	RD 0.06 (-0.06 to 0.18, Not reported	High§
			CBPS 267/355(75.2%)[a]		RD 0.08 (0.04 to 0.20), Not reported	
		Maternal retention 24m [a]	FBPS: 224/277 (80.9%)[a]	174/261 (66.7%)[a]	RD 0.13 (20.01 to 0.26), Not reported	
			CBPS: 216 /258 (83.7%)[a]		RD 0.16 (0.03 to 0.30), Not reported	
Richter, 2014	HIV+ pregnant recruited during pregnancy	4 or more ANC clinic visits (4 is standard practice) AT 1.5 months post delivery	328/**377** (87%)	355/466 (76.2)	2.17 95% CI 0.96 - 4.88, **p =0.062**	High§
Sam-Agudu, 2017	HIV+ pregnant, MIPS	maternal retention at 6 months postpartum	161/260 (61.9%)	59/ 237 (24.9%)	OR 5.2 95% CI 2.6 - 10.5, significant [b] aOR 5.9 95% CI 3.0 -11.6, significant [b]	Moderate€
POC CD4 TESTING AND CD4 COUNT–SPECIFIC ADHERENCE COUNSELLING						
Joseph, 2017	HIV+ pregnant	Retained at scheduled ART visits attended through first 12m on ART	304/603 (50.7)	295/547 (54.5)	RR = 0.93 95% CI 0.78 - 1.11, p= 0.426 aRR = 0.91 95% CI 0.77 - 1.07, p = 0.244	Some concerns§
VIDEO						
Kim, 2019	HIV+ pregnant women not on ART	retention ART clinic at 1 month	113/146 (77.4%)	120/160 (75%)	Not reported, p = 0.69	High¥

RR = risk ratio; aRR = adjusted RR; OR = odds ratio; aOR = adjusted OR; € = ROB assessed via ROBINS-II; § = ROB assessed via ROB 2 for cluster randomised trials; ¥ = ROB assessed via ROB 2 for individually randomised trials

a. Calculated by including women transferred out to numbers reported
b. Authors indicated p-value is significant but do not report the value
c. Authors indicated p-value is not-significant but do not report the value
d. *date taken from dataset provided in supplementary material filtered by control/ treatment, then endline, then in care)*

3.3.1 Pregnant and postpartum women

Overall, 11/23 studies evaluating interventions to improve retention in pregnant and postpartum women showed statistically significant effects. Table 2 demonstrates study reported retention data and Fig 3 provides recalculated OR's based on reported n/N's for studies with controls.

Only 2/6 peer support interventions showed statistically significant impacts on retention: structured mother mentor compared to routine unstructured sessions improved retention at 6 months [54]; and facility- versus community-based peer support compared to SOC improved retention at both 12 and 24 months postpartum [50]. Interventions showing high retention levels which were non-significant include; an enhanced intervention consisting of 8 peer mentor led sessions (4 ANC and 4 PNC) [52]. A cRCT of mother support groups [35], facility based versus community based peer support intervention [39], and a culturally adapted cognitive-behavioural intervention(CBI) led by mentor mothers [36] showed no significant difference between arms.

Maternal retention significantly improved in 4/5 mhealth interventions: maternal health information text messaging increased the number of ANC visits [32]; bi-directional text messaging resulted in improved attendance within 8 weeks post-delivery [47] but retention rates were low (19.6% intervention, 11.8% control); cellphone counselling improved retention at delivery and 6 weeks, but not 14 weeks, postpartum intervention compared to SOC arms [55]; and sending 14 messages during pregnancy and postpartum produced significant postpartum retention effects in the unadjusted model which did not persist when adjusted (Table 2) [48]. Cell phone based case management study showed high retention within 10 weeks and at 12 months post-delivery but sample sizes were small in both arms (n=50 each) and the difference in retention between arms was not significant[56].

Integration of ANC and HIV services was not statistically significant in improving retention in the first 6 months after HIV-positive diagnosis [57] but was at 12 months [59]. A model of care involving a series of interventions over three years to enhance linkage between ANC and ART showed significantly improved effects at 6 months [60]. No effect was seen in a 3 arm study

of integrated MIP clinics and integrated MIP clinics plus text messaging reminders compared to SOC at 12 months postpartum[44].

Both multicomponent interventions showed significant differences between arms; combining POC CD4 testing, task shifting, integrated MIP services and male and community involvement, increased MIP retention in intervention groups at both 6 and 12 weeks postpartum in all models [30]; and providing individualised PMTCT education, overarching service and personal support, and text and calls to issue visit reminders, resulted in a lower attrition of MIPS at 6 months postpartum [34].

Perinatal case management to provide support and address barriers to care, showed women in the intervention arm were significantly more likely to be retained in HIV care 12 months postpartum compared to those not receiving the intervention [31]. Conditional cash incentives for attendance of clinic visits and acceptance of PMTCT services [62] showed a significant 13% improvement in retention at 6 weeks postpartum.

CHWs for adherence counselling [46] and defaulter tracing [46, 58] between delivery and 60 to 120 days postpartum, CQI at 6 months postpartum [49] and point-of-care (POC) CD4 testing with CD4 count-specific adherence counselling[41] did not yield any significant improvement in retention.

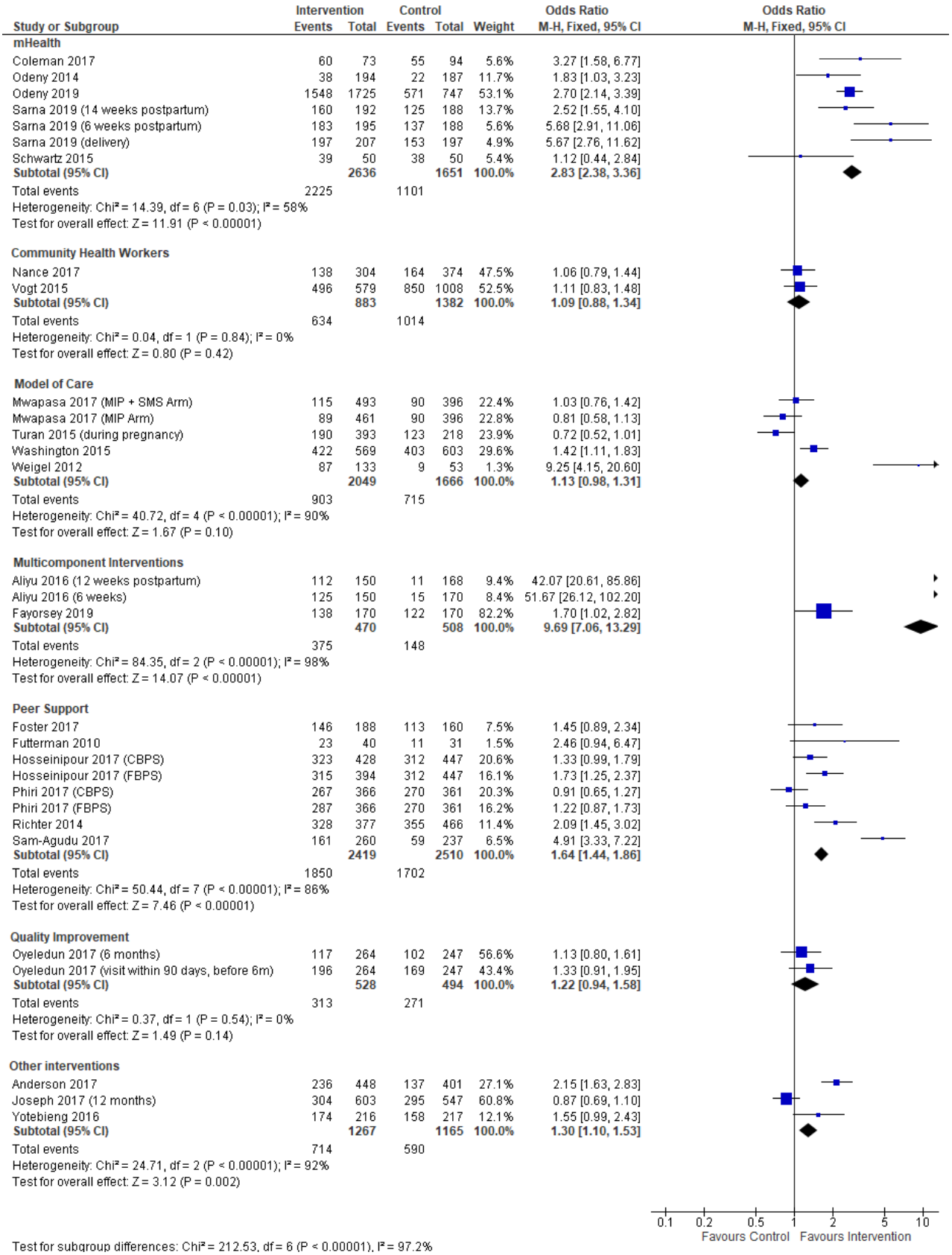


Figure 3: Effect of intervention type on retention in pregnant and postpartum women. Studies not using or reporting control date are not presented.

3.3.2 Pregnant women

For studies exploring retention in pregnant women only, 2/3 were significant, with all assessing short retention. A strong association was found between couple's HIV testing and counselling with male involvement at 1 month [61] and the Elombe SOP involving mentor mothers and defaulter tracing through text, calls and home visits showed women in intervention facilities were significantly less likely to miss second ANC visits [37] (Table 2 and Fig 4). A randomised pilot using a video based intervention showed no significant difference in retention at 1 month [42].

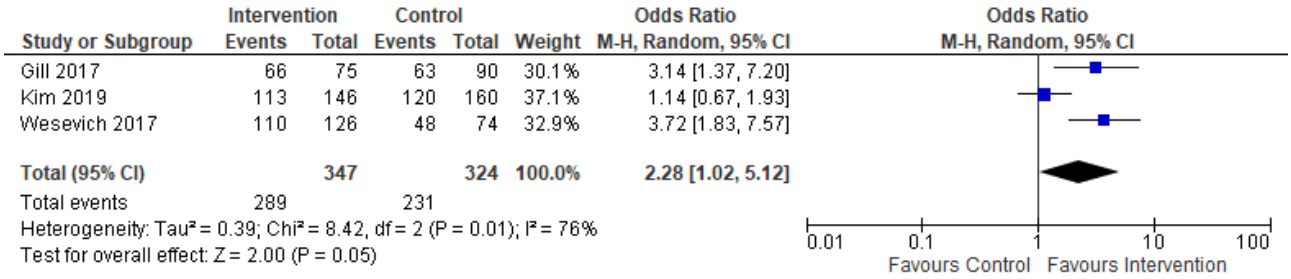


Figure 4: Effect of interventions on retention in pregnant women.

3.3.3 Postpartum women

Five studies focused on postpartum women only, with varied interventions, time points, settings and retention definitions. Three improved retention: Mother to Mother Uganda showed peer support [40] significantly improved MIP retention in intervention groups across 3 time points, 6 weeks post birth, 6 weeks post breastfeeding and at 18 months postpartum; integrated clinics for MCH services; integrated ART and MCH services improved 12 months postpartum maternal retention [63] and community outreach and paper based appointment tracking reported a net decrease of missed visits in intervention compared to control clinics at 6 months [53] (Table 2). However, for the latter recalculated ORs show those in the intervention were more likely to have missed visits that those in the control (Fig 5). Non-significant but high retention levels were observed for interventions involving lay health worker home visits [38] and postpartum adherence clubs [45] at 18 and 6 months' postpartum respectively.

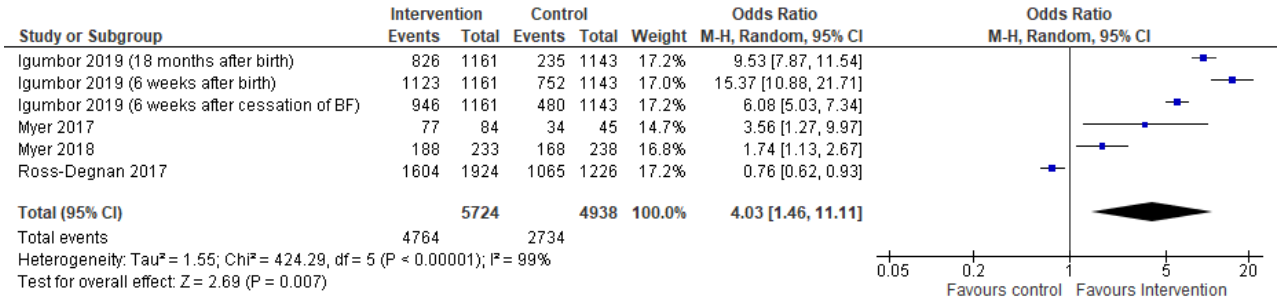


Figure 5: Effect of various interventions on maternal postpartum retention. Guillane 2017, a retrospective study with no control, is not presented.

3.4 Adherence

Pooled sample sizes for the 16 adherence studies were: 534 postpartum (n=2), 402 pregnant (n=2) and 4895 pregnant/postpartum women (n=12).

3.4.1 Pregnant and postpartum women

Table 4 demonstrates study reported effects and Fig 6 provides recalculated OR's based on reported n/N's for studies with controls. Overall, 2/12 interventions assessing adherence in pregnant and postpartum women showed statistically significant improvement in adherence: viral suppression was more likely before delivery, in the first 90 days post-delivery, and 12 months postpartum for the case management intervention although significance was only seen in the unadjusted model for the latter 2 timepoints [31] and structured Mentor Mother support was, at 6 months postpartum, associated with a higher likelihood of viral suppression [54].

It is worth noting that many studies demonstrated adequate to high levels of adherence although these were non-significant: high self-reported adherence at pregnancy and delivery in both Mamekhaya (95%) and control sites (100%) were observed (Table 2) but samples sizes were small with high LTFU among those recruited at baseline[36]; at 6 months postpartum, women in facility- and community-based peer support showed high rates of viral suppression (87% and 81%) [39]; and task shifting managed by ART nurses and peer counsellors instead of doctors with less frequent visits at 6 to 12 months postpartum showed adequate adherence (88%) although control group adherence was higher (91%) [43]. A peer led sessions of 4 ANC

and 4 PNC actually showed women in the SOC were significantly more likely to adhere to ARVs at 1.5 months postpartum than those in the intervention [52].

No significant improvement in adherence was found for: integrated care using self-report [57, 59]; multicomponent interventions measured by VL at 6 months postpartum [34]; facility and community based peer support[39]; CHWs using MPR at 90 days postpartum[46] financial incentives using pill count and viral load at 6 weeks [62]; and cognitive behavioural risk reduction individual and group sessions using self-reported at 12 months [51].

3.4.2 Pregnant women

Of the 2 studies evaluating improved adherence in pregnant women, a video intervention using pill count and self-report found a significant difference after 1 month when using a self-reported adherence measure, but none when using electronic pharmacy pill count [42]. However, adherence was extremely low at 13.6 – 15.3%. Using MPR, no association between cHCT and adherence measured by MPR was seen at 1-month post-ART initiation (Table 4 and Fig 7).

3.4.3 Postpartum women

Integration of ART and infant follow-up services showed a significant improvement in adherence measured by VL [63] for postpartum women. Adherence clubs showed no significant difference in viral suppression between arms at 3 time points but adherence levels were extremely high at 6 weeks (99%), 3 months (96%) and 6 months (95.2%) postpartum [45] (Fig 8).

Table 3: Characteristics of included studies for adherence in pregnant and postpartum women alphabetically by intervention type and author (n=16).

AUTHOR	COUNTRY	STUDY DESIGN	PERIOD OF DATA COLLECTION	ADHERENCE MEASURE	ADHERENCE ASSESSMENT TIMEPOINTS	POPULATION	INTERVENTION DESCRIPTION	CONTROL DESCRIPTION
ADHERENCE CLUB								
Myer, 2017	South Africa	cohort	February to September 2015	VL <50, 50 - 1000 and >1000 copies/ml	6weeks, 3 and 6 months postpartum	postpartum	Described in retention table	Described in retention table
CASE MANAGERS								
Anderson, 2017	USA	retrospective	2005 to 2013	VL ≤200 copies/mL closest to delivery during pregnancy	HIV care engagement within 90 days' post-delivery and 12m	pregnant women, postpartum, MIPS	Described in retention table	Described in retention table
COGNITIVE BEHAVIOURAL RISK REDUCTION								
Ramlagan, 2019	South Africa	cRCT	April 2014 to March 2017	Self-reported maternal ARV use	12 months		'Protect Your Family' (PYF) participants received SOC PMTCT and lay health worker led group and individual theory-based social- group intervention sessions during pregnancy and postpartum.	SOC PMTCT care and health videos to ensure SOC participants were at the facility for the same duration as intervention participants
COMMUNITY HEALTH WORKERS								
Nance, 2017	Tanzania	cRCT	May 2015 to March 2016	medication possession ratio (MPR) ≥ 95%	60 -120 days postpartum	pregnant, postpartum	Described in retention table	Described in retention table
COUPLES HIV TESTING AND COUNSELLING								
Wesevich, 2017	Malawi	observational	March to September 2014	Adherence ≥90% within 33 days (calculated by clinicians, as number of pills taken/ number of days elapsed)	within 33 days post ART initiation	pregnant	Described in retention table	Described in retention table
FINANCIAL INCENTIVE								
Yotebieng, 2016	DRC	RCT	April 2013 to August 2016	pill count (100% adherence) and VL	pill count monthly, VL at enrolment, delivery, 6 and 8 weeks postpartum	pregnant, postpartum	Described in retention table	Described in retention table
MODEL OF CARE								
Myer, 2018	South Africa	RCT	June 2013 to December 2014	VL <50 and <1000 copies/ml	12 months postpartum	postpartum	Described in retention table	Described in retention table
Turan, 2015	Kenya	cRCT	June 2009 to March 2011	self-reported maternal ARV use during pregnancy	ARV use during pregnancy, labour and delivery, postpartum	pregnant, postpartum	Integrated care at ANC AND HIV care and treatment in the same clinic until 18 months postpartum)	ANC referral for HIV care at same facility but a different clinic
Washington, 2015	Kenya	cRCT	June 2009 to March 2011	self-report, swallowed ARVs for PMTCT across antepartum, intrapartum, and postpartum periods	12 months after enrolment	pregnant, postpartum	Combined ANC, PMTCT, and HIV services in same clinic. Same clinician provided ANC and postpartum services including EID until confirmed infant HIV diagnosis or infant 18m old. HIV+ MIPs referred to long-term care at facility's HIV clinic.	routine ANC and PMTCT services per National Guidelines. Once diagnosed, HIV infected women given referral to HIV care.
MULTICOMPONENT INTERVENTIONS								
Fayorsey, 2019	Kenya	RCT	Sep 2013 to 2015	women retained with VL <1000 copies/mL	6 months postpartum	pregnant, postpartum	Described in retention table	Described in retention table

PEER SUPPORT								
Futterman, 2010	South Africa	pilot cohort	2006 to 2007	Medication use during pregnancy (unclear how measured, possibly from health records)	6 months postpartum	pregnant, postpartum	Described in retention table	Described in retention table
Hosseinipour, 2017	Malawi	cRCT	Not reported	VL suppressed <1000 copies/ml at 6m	6 months	pregnant, postpartum	Described in retention table	Described in retention table
Richter, 2014	South Africa	cRCT	July 2008 to April 2010	Mother took AZT from the 28th week of pregnancy, or on HAART	1.5 months post birth	pregnant, postpartum	Described in retention table	Described in retention table
Sam-Agudu, 2017	Nigeria	cohort	April 2014 to September 2016	VS VL <20 copies/ml	6 months postpartum	pregnant, postpartum, MIPS	Described in retention table	Described in retention table
TASK SHIFTING								
Kiweewa, 2013	Uganda	RCT	May 2007 to September 2009	VL < 400 copies/ml	6 – 12 months post ART initiation	pregnant, postpartum	Less frequent visits mostly managed by ART nurse and peer counsellor, ART nurses managed most follow-up visits at longer intervals between visits, patients supported by peer counsellors and home visiting	SOC (monthly ART care by doctor, routine counselling by certified nurse counsellor. No home visits in case of missed visits.
VIDEO								
Kim, 2019	Malawi	randomised pilot	December 2016 to February 2018	electronic pharmacy pill count > 90–100%	1 month	pregnant	Described in retention table	Described in retention table

Table 4: Results and effect sizes reported by included adherence studies in pregnant and postpartum women by intervention.

AUTHOR	LENGTH OF FOLLOW UP	POPULATION PREGNANT/POSTPARTUM	OUTCOME MEASURE	INTERVENTION %	CONTROL %	EFFECT SIZE, 95% CI, P-VALUE	ROB
ADHERENCE CLUBS							
Myer, 2017	6months postpartum	postpartum women	Combined <1000 copies at 6 weeks	80/81 (99%)	42/42 (100%)	Not reported, p=0.483	Serious€
			Combined <1000 copies/ml 3 months postpartum	75/78(96%)	35/36(97%)		
			Combined <1000 copies/ml 6months postpartum	71/77 (92.2%)	29/33 (87.9%)		
CASE MANAGERS							
Anderson, 2017	12 months	HIV+ postpartum and HIV exposed infants	VL ≤200 copies/mL closest to delivery during ANC	301/448 (67.2%)	167/401 (41.7%)	OR 3.02 95% CI 2.26-4.05, p **< 0.0001** aOR 1.90 95% CI 1.33-2.71, **p = 0.0005**	Serious€
			min one VL or CD4 count test in first 90-days after delivery	192/448 (42.9%)	142/401 (35.4%)	OR 1.36 95% CI 1.03-1.80, **p = 0.029** aOR 1.21 95% CI 0.88-1.65, p = 0.236	
			VL ≤200 copies/mL at 12 months post-delivery	184/448 (41.1%)	119/401 (29.7%)	OR 1.73 95% CI 1.30-2.30, **p = 0.0002** aOR 1.26 95% CI 0.90-1.77, p =0.178	
COGNITIVE BEHAVIOURAL RISK REDUCTION							
Ramlagan, 2019	12 months after birth	HIV+ 8 - 24 weeks pregnant and postpartum	self-reported maternal adherence to ART	143/196 (72.9%)	202/220 (91.8%)	Not reported	Some concerns§
COMMUNITY HEALTH WORKERS							
Nance, 2017	90 days postpartum	HIV + pregnant and postpartum, MIPS	MPR ≥ 95%	41/138 (29.7)	39/164 (23.8%)	Not reported	High§
COUPLES HIV TESTING AND COUNSELLING							
Wesevich, 2017	1 month	HIV+ pregnant women	Adherence ≥90% within 31 days (calculated by clinicians, as number of pills taken/ number of days elapsed)	76/110(69%)	32/48(67%)	RR 1.04 95%CI 0.82 – 1.31, p= 0.8 aRR 1.01 95% CI 0.80 – 1.27, p = >0.9	Moderate€
FINANCIAL INCENTIVE							
Yotebieng, 2016	8 weeks postpartum	newly diagnosed HIV+ ≤32 weeks gestational age	Adherence to ARVs based on pill count	109/156 (69.9%)	96/141 (68.1%)	RD 0.02 95%CI -0.06 to 0.09, p not reported aRD 0.03 95%CI -0.05 to 0.12, p not reported	Some concerns¥
			6 weeks postpartum VL, undetectable	113/171 (66.1%)	108/155(69.7%)	risk difference, -0.04; 95% CI: -0.14 to 0.07, P Not reported	
MULTICOMPONENT INTERVENTIONS							
Fayorsey, 2019	6 months	HIV+ starting ANC	women retained with VL <1000 copies/mL	99/170 (58.2%)	86/170 (50.6%)	RR 1.1.5 95% CI 0.95–1.40, p = 0.16	Low¥
			women retained with VL < 40 copies/ mL	84/170 (49.4%)	69/170 (40.6%)	RR 1.22 95% CI 0.96–1.54, p = 0.10	
MODEL OF CARE							
Myer, 2018	12 months postpartum	HIV+ postpartum	<1000 copies/ml	162/202 (780%)	142/209 (68%)	Not reported, p = 0.005	Low¥
Turan, 2015	6 months postpartum	HIV+ pregnant	self-reported ARV use during pregnancy	138/173 (80%)	75 /152 (49%)	OR 4.05 95% CI 2.00 to 8.00, Not reported	High§
			self-reported ARV use during labour and delivery	28/173 (16%)	84/152 (55%)	OR 0.16 95%CI 0.04 to 0.68, Not reported	
			self-reported maternal and infant ARVs use post birth	22/173(13%)	57 /152 (38%)	OR 0.24 95%CI 0.08 to 0.70, Not reported	
Washington, 2015	12 months after enrollment	HIV+ pregnant	Self-report of swallowed ARVs across antepartum, intrapartum, and postpartum periods	37/176 (21%)	23/153 (15%)	OR 1.72 95% CI 0.85 - 3.48, not significant [d]	High§

			Self-report of swallowing only intrapartum and postpartum ARVs (incomplete PMTCT intervention)	19/176 (11%)	60/153 (40%)	OR 0.39 95% CI 0.11 - 1.36, not significant [d]	
PEER SUPPORT							
Futterman, 2010	6 months post delivery	HIV+ pregnant	Self-report used medication during pregnancy	38/40 (95%)	31/31 (100%)	Not reported	Serious€
			Sel-report used medication during delivery	37/40 (92.5%)	30/31 (96.8%)	Not reported	
Hosseinipour, 2017	6 months	HIV+ pregnant	VL < 1000 Copies/ml FBPS	237/274(87%)	208/247 (84%)	Not reported, p = 0.20	High§
			VL < 1000 Copies/ml CBPS	254/312 (81%)			
Richter, 2014	1.5 months post delivery	HIV+ pregnant	Mother took AZT from 28th week of pregnancy, or on HAART[a]	340/377 (90.2%)	445/466 (95.5%)	OR 0.44 95% CI 0.26 - 0.74, p = 0.002	High§
Sam-Agudu, 2017	up to 6 months postpartum	HIV+ pregnant, MIPS	VL <20 copies/ml for women with VL results available	108/176 (61.4%)	22/48 (45.8%)	OR = 7.4 95% CI 3.8 - 14.5, significant [c] aOR = 4.9 95% CI 2.6 - 9.2, significant [c]	Moderate€
TASK SHIFTING							
Kiweewa, 2013	6 to 12 months post ART initiation	pregnant and postpartum	VL < 400 copies/Ml	38/43 (88%)	29/32 (91%)	Difference (95% CI) -0.03 (12% to 11%), Not reported	Low¥
VIDEO							
Kim, 2019	1 month	HIV+ pregnant not on ART	electronic pharmacy pill count > 90–100%	95/146 (65.1)	95/160 (59.4)	Not reported, p =0.31	High¥
			Self-reported adherence at one-month: missed dose in past 7 days	16/117 [b] (13.6%)	34/127 [b] (26.8%)	Not reported, p =0.02	
			Self-reported adherence at one-month: missed dose in past 30 days	18/117 [b] (15.3%)	38/127 [b] (29.9%)	Not reported, p = 0.02	

€ROB assessed via ROBINS II

§ ROB assessed via ROB 2 for cluster randomised trials

¥ ROB assessed via ROB 2 for individually randomised trials

a. unclear how this was measured, possibly extracted from health records
b. calculated denominator
c. indicated as significant, but p-value not reported
d. indicated as non-significant, but p-value not reported

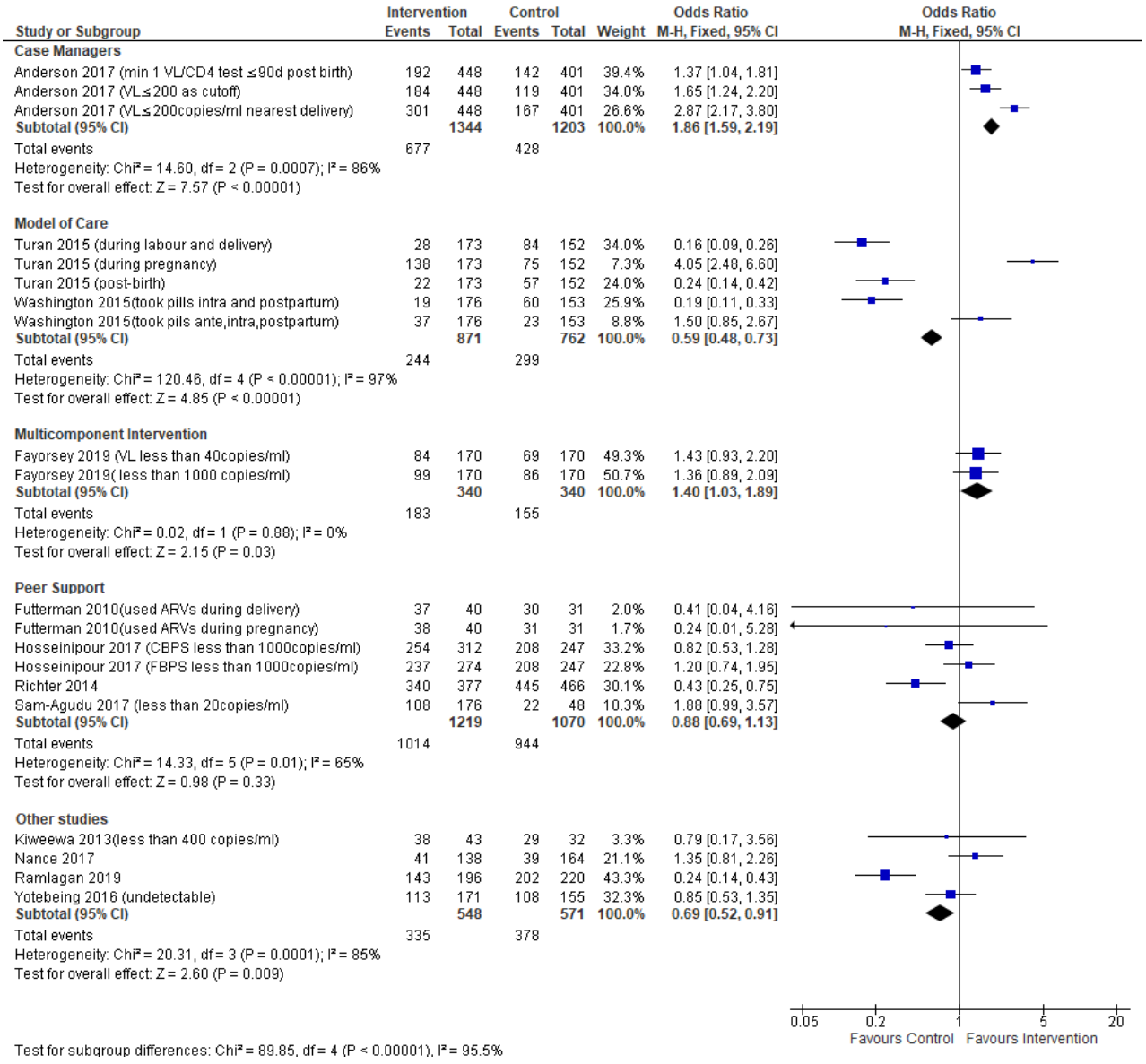


Figure 6: Recalculated effects of interventions on adherence in pregnant and postpartum women.

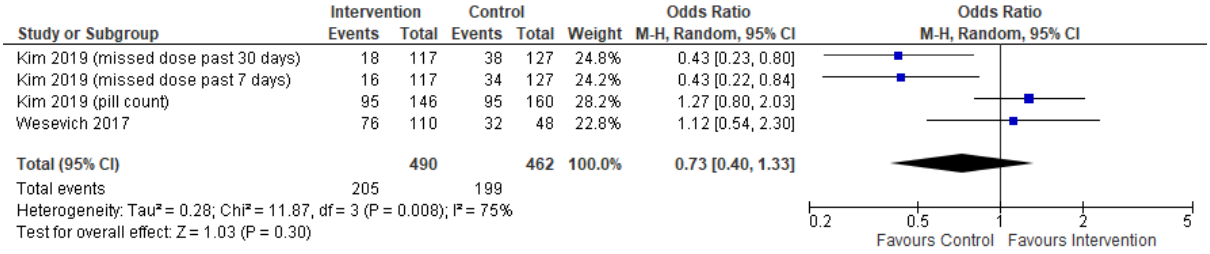


Figure 7: Effect of intervention on ART adherence in pregnant women, across various time points and adherence measures.

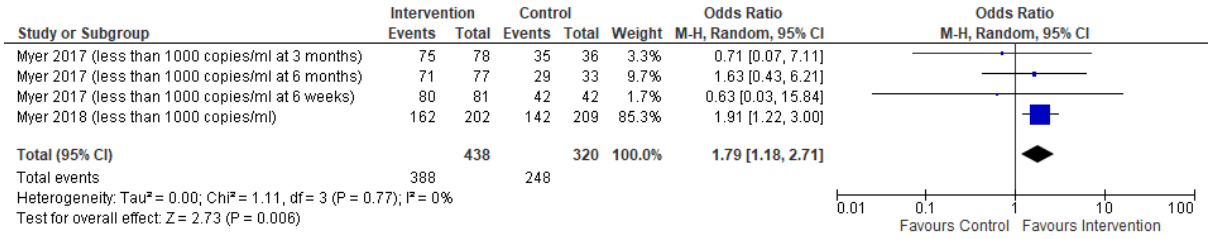


Figure 8: Effect of intervention on ART adherence in postpartum women, across various time points and adherence measures.

3.4.4 Adherence measure categories

Five studies used objective measures, 5 subjective measures and 6 used biological correlates of VL to assess adherence (Table 4 and Fig 9), with some studies using more than 1 measure to assess adherence. Fig 9 indicates that the subjective self-report measures favours the control, but the objective adherence measures and VL favours intervention.

Objective measures included electronic pharmacy pill count (n=3), and medication possession ratio (n=2). All cut offs across measures was at ≥90% adherence except for one study using proportion of days covered which used ≥80%. The only subjective measure used was self-report, without specification of the tools used, where women reported ARV usage across a wide range of time points; during pregnancy (n=1), labour(n=1), delivery (n=1), postpartum (n=1), 1.5 months after birth (n=1), 6 months postpartum (n=1) and 12 months postpartum (n=1). All studies involving adherence self-report after an intervention involved pregnant women followed up in to postpartum.

Eight studies used VL as a biological correlate to measures adherence in pregnant and postpartum women. Cut-offs were wide ranging at <20, <40, <50, 50 – 1000, ≤200, <400, <1000 copies/mL and undetectable VL with some studies measuring adherence at multiple cut-off points. Time points at which VL was assessed were also wide ranging from within 90 days post-delivery (n=1) 6 weeks (n=2), 3 months (n=1), 6 months(n=5) and 12 months (n=3). The most common time point and VL cut-off used across adherence studies was 6 months and <1000 copies/ml respectively. Two studies focused on postpartum women, and the remaining 6 involved pregnant women or MIPS followed in to the postpartum period.

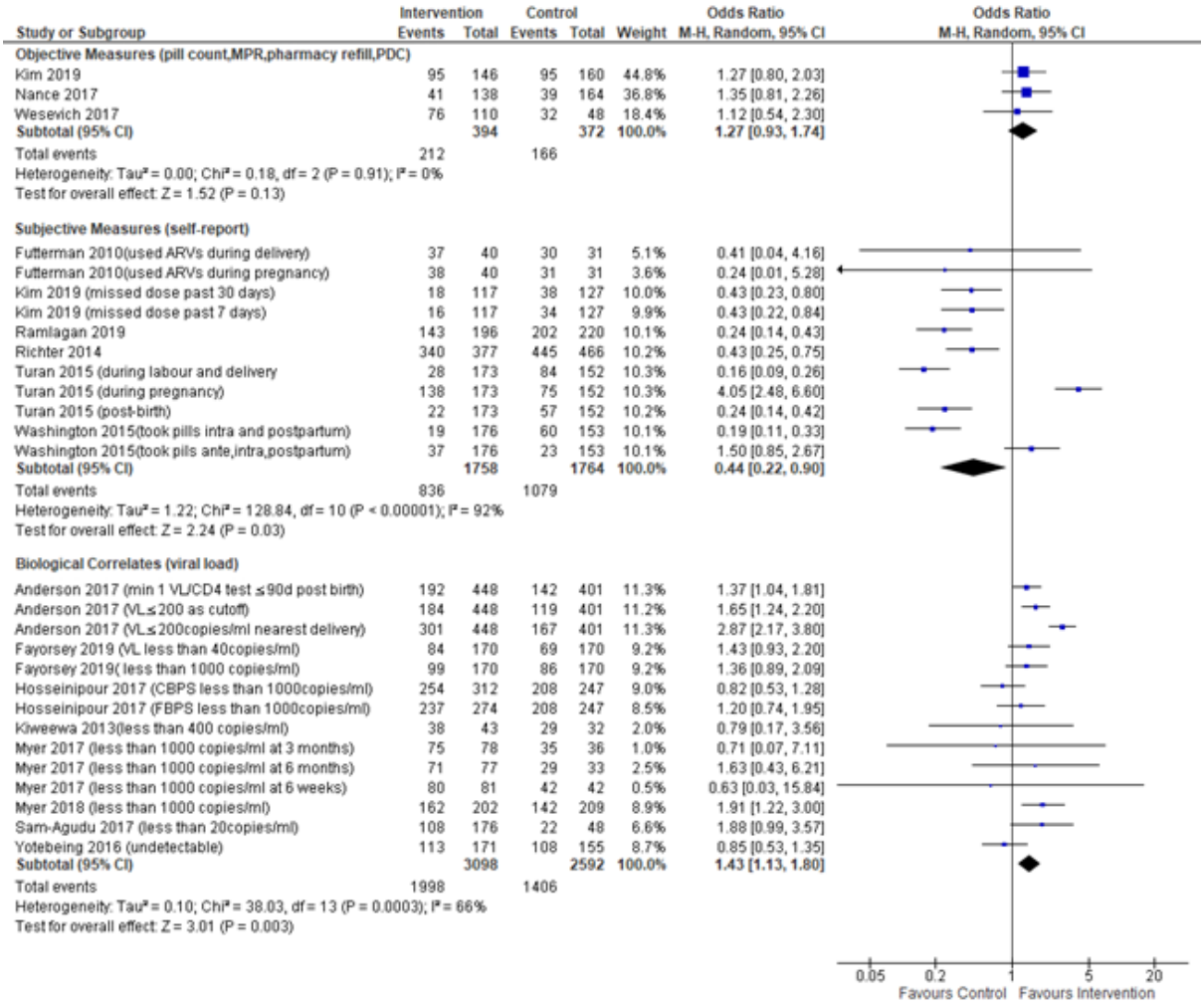
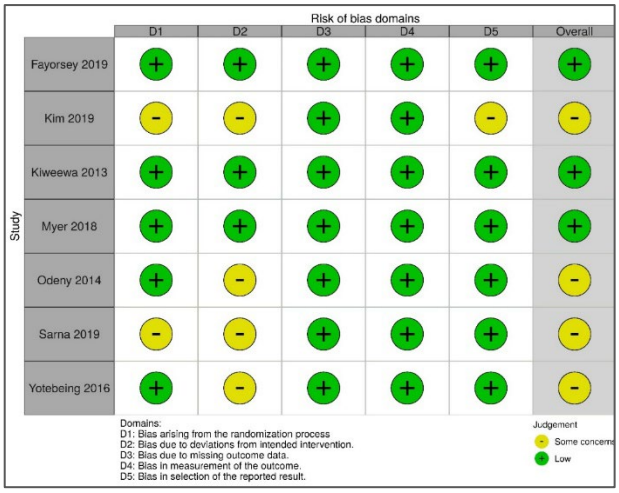


Figure 9: Recalculated effects sizes of study interventions outcomes categorised by adherence measures categories and cut-offs.

3.5 Risk of Bias

Eight of 15 cRCTs were of high risk, 7 had some concerns and none were of low risk (Figs 10a, 10b and 11). High risk resulted from timing of identification and recruitment of participants after cluster randomization and lack of information on randomization method and lack of blinding. Three of the 7 RCTs were of low risk, 4 were rated as having some concerns, and none were of high risk. Similar to cRCTS bias arose from lack of blinding and allocation concealment information. Using ROBINS-I, 2 studies were of moderate risk, 8 of high risk and 1 of critical risk of bias, arising mainly from confounding, selection of the reported result and lack of information on intervention deviations (Figs 12a and 12b). No studies were excluded on the basis of quality to provide a holistic view of intervention findings in the narrative.

10a.



10b.

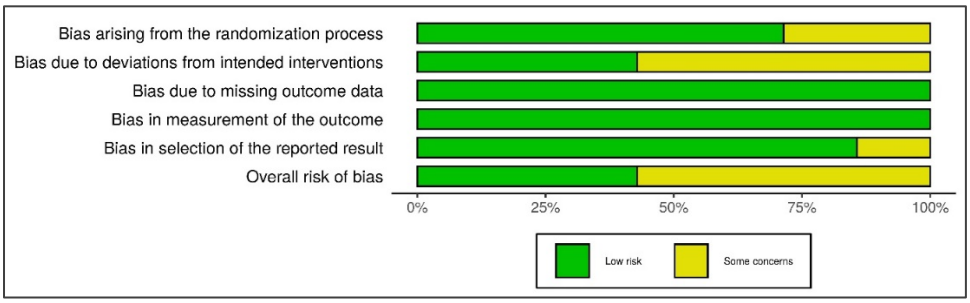


Figure 10: Risk of bias assessment for randomised control trials using ROB 2 by a) study and b) weighted plots by domain.

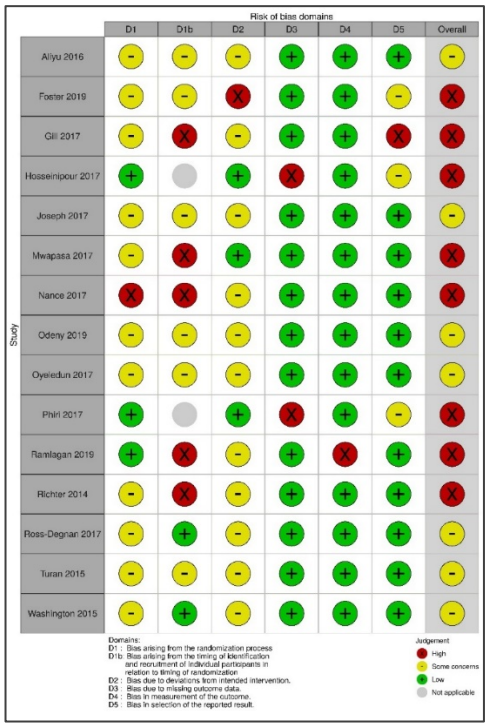
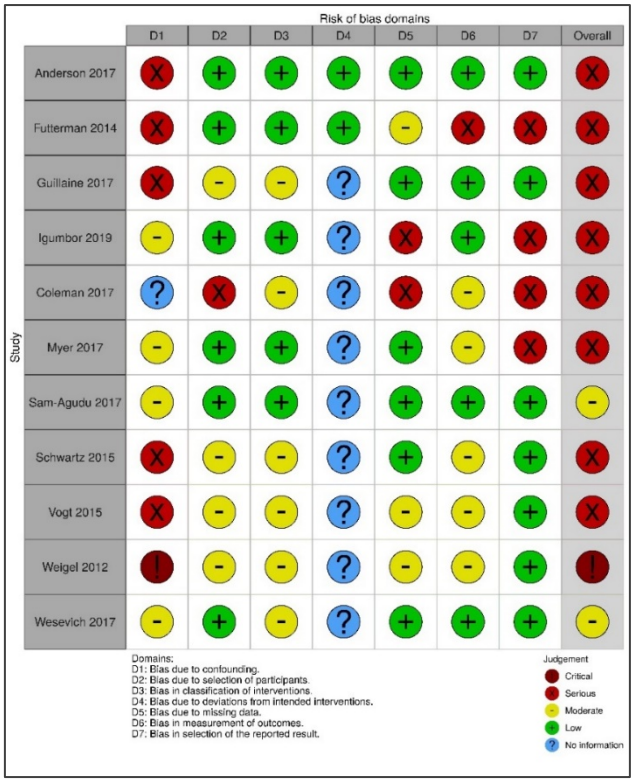


Figure 11: Risk of bias assessment for studies with a cluster-randomised and stepped wedge study design using ROB 2. Diagrams were generated with the official ROBVIS tool, which does not generate weighted plots for cluster-randomised trials.

12a.



12b.

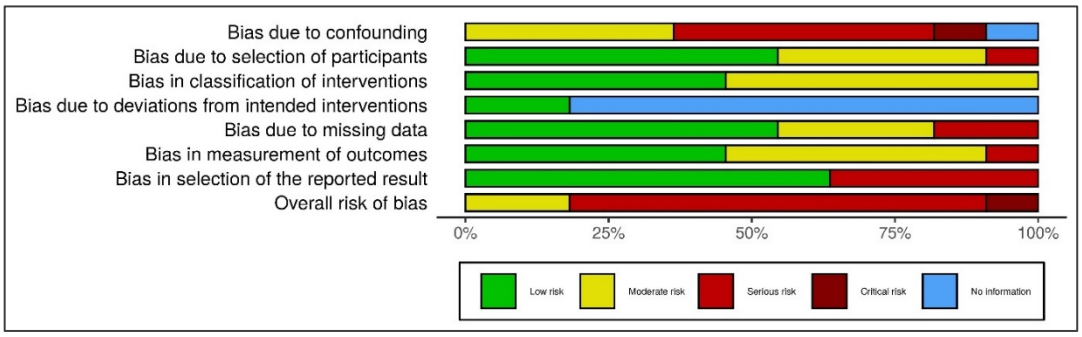


Figure 12: Risk of bias assessment for non-randomised control trials using ROBINS by a) study and b) weighted domain.

3.6 PRECIS-2

The majority of PRECIS-2 scores were between pragmatic and equally pragmatic/explanatory on the continuum (Table 6). Average scores for each study indicated that all were either equally pragmatic and explanatory (scores 3.0 to 3.9) or pragmatic (scores 4.0 to 5.0), except for a cHTC study that was rated 2.9 at the explanatory level (scores 1 to 2.9).

Analysis by intervention type showed that two SMS based maternal health interventions, a video intervention and multicomponent interventions were equally pragmatic and

explanatory while integrating of MCH services, financial incentives and a structured peer mother program were the most pragmatic. The only study scored as rather explanatory was a cHTC study, involving one facility, recruitment of males by invites and specific study tracing and follow-up. Overall 18 studies were scored as rather pragmatic to implement in practice.

3.7 Ongoing studies identified

The search process identified 18 ongoing RCTs with our relevant outcomes (S3 Table). This list is non-exhaustive consisting of 14 ongoing studies exploring retention, and 13 assessing adherence in pregnant and postpartum women. Intervention types are varied including: a smartphone application; video; electronic pill container triggering text messaging if unopened; peer support (n=6); male involvement and couples counselling (n=2); 2 CQI interventions and text message interventions each; a behavioural parenting programme; depression support group and group counselling; an adherence club, and community leader engagement. Outcome assessment time points ranged from 3 to 24 months.

Table 5: Mean PRECIS-2 scores of for each study and across domains.

Study ID	Intervention	1 Eligibility	2 Recruitment	3 Setting	4 Organisation	5 Flexibility (delivery)	6 Flexibility (Adherence)	7 Follow- up	8 Outcome	9 Analysis	Mean (SD)
Wesevich 2017[c]	cHCT	4	2	1	2	2	2	3	5	5	**2.9 (1.5) ***
Coleman 2017[a]	mHealth	4	NA	5	1	2	3	4	5	3	**3,4 (1,4) ***
Kim 2019[c]	video	2	5	5	1	4	NA	2	5	4	**3,5 (1,6)**
Ross-Degnan 2017[c]	Appointment tracking	3	5	5	3	1	4	3	5	3	**3.6 (1.3)**
Fayorsey 2019[c]	Multicomponent	4	5	5	1	2	3	2	5	5	**3,6 (1,6) ***
Nance 2017[c]	CHWs	4	NA	3	2	4	4	4	5	3	**3,6 (0.9)**
Sarna 2019[a]	mHealth	3	5	5	2	3	4	2	5	4	**3.7 (1.2)**
Odeny 2014[a]	mHealth	3	5	5	2	2	4	3	5	4	**3,7 (1.2) ***
Richter 2014[c]	Peer Support	5	5	3	2	2	4	3	5	4	**3,7 (1,2) ***
Gill 2018[a]	Multicomponent	4	5	5	2	2	3	3	5	5	**3,8 (1,3) ***
Odeny 2019[a]	mHealth	5	5	3	2	2	4	3	5	5	**3,8 (1,3) ***
Oyeledun 2017[a]	QI	4	4	4	1	1	5	5	5	5	**3,8 (1,6)**
Aliyu 2016[a]	Multicomponent	4	5	5	1	2	4	4	5	5	**3,9 (1,5) ***
Hosseinipour 2017[c]	Peer Support	5	5	5	2	3	3	4	5	3	**3,9 (1,2)**
Myer 2017[c]	Adherence Club	2	5	5	3	4	4	3	5	4	**3,9 (1,1)**
Turan 2015[c]	Model of Care	5	5	4	1	1	5	4	5	5	**3,9 (1,7)**
Weigel 2012[a]	Model of Care	5	5	5	1	1	5	4	5	4	**3,9 (1,7)**
Foster 2017[a]	Peer Support	5	5	5	2	2	2	5	5	5	**4,0 (1,5)**
Joseph 2017[a]	POC CD4 testing and count–specific adherence counselling	5	5	4	1	2	NA	5	5	5	**4,0 (1,6)**
Phiri 2017[a]	Peer Support	5	5	5	2	3	3	4	5	4	**4,0 (1,1)**
Schwartz 2015[a]	mHealth	4	5	3	3	3	4	4	5	5	**4,0 (0,9)**
Vogt 2015[a]	CHWs	5	5	5	3	3	4	2	5	4	**4,0 (1,1)**
Washington 2015[c]	Model of Care	5	5	5	1	1	5	5	5	5	**4,1 (1,8)**

Study ID	Intervention	1 Eligibility	2 Recruitment	3 Setting	4 Organisation	5 Flexibility (delivery)	6 Flexibility (Adherence)	7 Follow- up	8 Outcome	9 Analysis	Mean (SD)
Mwapasa 2017[a]	Model of Care	3	5	5	3	4	4	4	5	5	**4,2 (0,8)**
Ramlagan 2019[b]	cognitive behavioural risk reduction	4	5	5	3	2	5	5	5	4	**4,2 (1,1)**
Yotebieng 2016[c]	Financial Incentive	5	5	5	3	3	2	5	5	5	**4,2 (1,2)**
Anderson 2017[c]	Case managers	4	5	5	5	5	3	2	5	5	**4,3 (1,1) ***
Futterman 2010[c]	Peer Support	5	5	5	3	2	5	5	5	4	**4,3 (1,1)**
Igumbor 2019[a]	Peer Support	5	5	5	3	4	4	3	5	5	**4,3 (0,9) ***
Kiweewa 2013[b]	Task shifting	3	5	5	3	4	4	5	5	5	**4,3 (0,9)**
Guillaine 2017[a]	Multicomponent	5	NA	3	3	5	5	4	5	5	**4,4 (0,9)**
Sam-Agudu 2017[c]	Peer Support	5	5	5	3	3	4	5	5	5	**4,4 (0,9) ***
Myer 2018[c]	Model of Care	3	5	4	4	5	5	5	5	5	**4,6 (0,7) ***
Mean (SD)		**4,2 (1.0)**	**5,0 (0.2)**	**4,6 (0.8)**	**2,3 (1.0) [d]**	**2,8 (1.2) [d]**	**4,0 (0.9)**	**3,8 (1.1)**	**5,0 (0.0)**	**4,4 (0.7)**	3.9 (1.2)

Scores: 1 = Very explanatory, 2 = Rather explanatory, 3 = Equally pragmatic/explanatory, 4 = Rather pragmatic, 5 = Very pragmatic.

a. Retention
b. Adherence
c. Retention and adherence
d. Explanatory
e. Pragmatic

* statistically significant outcomes

4 DISCUSSION

This systematic review identified 33 studies assessing the effect of interventions on retention in care and adherence to ART during ANC and PNC, with none identified for ICC or PCC periods. All published articles were conducted between 2010 and 2019, the most (n= 14) being in 2017, possibly related to earlier recommendations highlighting the need for tailored interventions [2, 6, 10] for these population groups.

All interventions were conducted in sub-Saharan Africa, except one from the USA. This absence of regionally diverse data is surprising given that countries in Asia such as Thailand, India and China have high numbers of PLWHIV [64]. It is possible our search strategy may have not identified these studies, however ongoing studies show a similar pattern. Intervention types were varied and significant heterogeneity was found in intervention complexity, study design, outcome definition, outcome measurement, assessment time points, as well as intensity and duration of follow-up.

The majority of interventions recruited women during ANC and followed them through to the postpartum period, varying over duration of follow-up and time points. Peer support, mhealth, models of care, multicomponent interventions, financial incentives, cHCT and case management significantly improved retention, in contrast to one peer support, model of care and case management intervention each which were associated with significantly improved adherence.

Although the most frequent intervention type, only one peer support intervention [54] recruiting women during ANC with follow-up into postpartum, demonstrated significant benefit, involving relatively short term retention at 6 months postpartum and finding low retention estimates (61.9%). Considering the postpartum period, one peer support mentor mother intervention with large MIPS sample sizes showed significantly high levels of retention at 6 weeks after birth, 6 weeks after cessation of breastfeeding and long term at 18 months post-delivery [40]. Although reduced retention was still observed along these time points, the study shows promise as a successful intervention for adoption and scale up. Following up women at different time points from short to longer term can uncover finer granularity in

early patterns of retention [65]. Peer support can promote care seeking behaviour by addressing psychosocial barriers to care and stigma [66] but privacy concerns could be a hindrance to wide scale implementation [67].

mHealth, particularly text messaging and cellphone counselling, showed promise as a strategy to improve retention with almost all demonstrating significantly improved outcomes and high retention estimates ranging from 82.2% to 95.2%, although these were at short term retention periods. Twice-weekly text messages relevant to pregnancy stage also improved ANC retention although sample sizes were small [32]. Bi-directional text messaging and calls between women and the facilities also improved short term retention levels at 8 weeks post-delivery [48]. However, issues such as overt or covert content of text messages [68] for those who share phones and the uncertainty of whether women actually read messages sent [69] require further examination given the challenges of time and stigma this population cite as barriers to care. Another intervention showing improved short term retention at delivery and 6 weeks postpartum was cellphone counselling [55]. Retention at the 14 week timepoint for this same study was not significant but still high at 83.3% but as expected displayed a drop in retention compared to the earlier timepoints. More evidence is needed at long-term retention points for this intervention type.

Almost all multicomponent interventions showed significantly improved effects (ranging from 75% to 83%). However, this was again at mainly short-term retention timepoints. A significantly large effect size was seen on MIP retention at 6 and 12 weeks in rural Nigeria after a combined package of task shifting from doctors to nurses midwives and CHWs, POC CD4 testing, integrated mother and infant care, family or male partner participation in care and community engagement [30]. Other multicomponent interventions [34, 37] used varied combinations of lay counsellors or mentor mothers to provide phone and text visit reminders, defaulter tracing by home visits, counselling, home or clinic PMTCT health education. This led to decreased MIP attrition 6 months postpartum [34] and improved retention in early ANC [37] - however the latter used small sample sizes and only measured outcomes between the first and second ANC visit making it too weak to base recommendations on. Even though not significant, another study demonstrated high long-term 18-month retention (99.5%)[38]. While demonstrating improvements, this intervention type could be resource intensive and

logistically costly, and scored on the less pragmatic side of the PRECIS-2 scale. Nevertheless, it remains a valuable strategy with potential for improving retention in both pregnant and postpartum women in the short and longer term, with more work needed on the latter.

The impact of integration of services as a model of care intervention on retention remains uncertain based on gathered evidence. PNC integration of MCH and ART service showed significantly higher retention 12 months postpartum and was scored most pragmatic for real world settings, highlighting its potential for further study and adoption. This is different from earlier studies of integration of ANC and ART care in Kenya [57, 59] which did not echo this finding. This may be due to the heterogeneity in context, content of services, type of staff delivering services (nurse-midwives versus clinicians), and retention or loss-to-follow-up definitions. Another model of care aiming to improve linkage of service between ANC and ART clinics showed significantly improved 6-month retention relative to the control but at low levels (65%) with the study itself showing critical ROB. While service integration targets multiple barriers to ANC, PNC and HIV care such as cost and time constraints, Turan *et al*. 2015 [57] question whether integration of HIV care may place additional burdens on already overworked, under resourced HCWs and poor infrastructure [57, 70]. One study [44] encountered resistance during implementation from HCWs due to increased workloads resulting from integration, which was resolved in part by incentives. However, for scale up and implementation this would not be sustainable. Women have also raised concerns about service integration leading to overcrowded facilities and mothers and infants both being attended to on visit days [71].

One intervention using financial incentives [62], which increased at each subsequent visit, significantly improved retention at 6 weeks postpartum, for women recruited during ANC. This intervention type may address patient level costs barriers to visit attendance, although the health system cost may be a hindrance to scale up in certain contexts.

Case management during ANC and postpartum [31] appointment tracking postpartum [53], and cHTC during pregnancy [61] are also worthy strategies to consider to improve maternal retention. The case management intervention while rated as high ROB and showing moderate retention levels (52.7%) 12 months postpartum in the USA, may be valuable in that case

managers provided referrals, psychosocial support and address individual barriers to care. Since not all pregnant and postpartum women will face the same set of challenges, this intervention offers individually tailored support.

It is worth noting that, although non-significant, many studies looking at long-term time points showed high levels of retention. This is important given the absence of assessment of long term retention noted in previous reviews [5, 20]. Peer support [50] was assessed long term at 12 and 24 months, although this was post-ART initiation and not postpartum, showing high retention (80.9% and 83.7%). Surprisingly 24-month retention was higher than that at 12 months. Similarly, almost 100% retention at 18 months postpartum was found in an multicomponent intervention [38]. While single interventions showed promised, they may be insufficient individually to promote improved maternal health outcomes. Combined interventions could be the answer but more evidence is needed to make definitive recommendations.

Overall, the evidence for interventions to improve adherence in pregnant and postpartum women were weak. More interventions focussed on improving retention in care rather than ART adherence in our populations of interest (33 versus 16 studies respectively). Fourteen studies assessing retention assessed ART adherence as well, but only 2 explored adherence specifically. While retaining pregnant and postpartum in care is important there is a distinction between women attending visits [65] and actually being ART adherent. Said another way “adherence” to scheduled visits does not translate to adherence to ART, so this finding highlights the need for more interventions to improve ART adherence particularly since only 3 studies demonstrated >90% adherence[36, 45, 52] and 4 showed ≥80 – 90 % adherence[39, 43, 57], none of which were significant. Using VL data, integration of services [63], case management at delivery and 12 months post-delivery [31], and structured peer support programs [54] showed significantly improved adherence but these were at low levels (41.1% to 78%). However, these 3 interventions were also those that produced a significant effect on retention. This indicates that use of these intervention types may serve a dual purpose and address improvement in both outcomes in our populations of interest.

A few peer support interventions demonstrated >90% adherence with one finding women in the SOC were significantly more adherence than those in the intervention [52]. Task shifting [43] and cognitive behavioural risk reduction[51] were 2 interventions exploring adherence only at between 6 to 12 months. While neither were significant both showed high adherence in the control compared to the intervention groups, one using VL [43] and the other self-report [51].

In terms of adherence measures, most studies used VL as a biological correlate to assess adherence although self-report usage was also high. Studies using the latter subjective measure did not specify the tools used for self-report or whether these were validated, adding another layer of variability to a measure that is already inconsistent due to its high risk of social desirability and recall bias.

The need for standardized measures for cross comparability and reproducibility, and evidence of long-term efficacy has been underscored before for both retention [72] and adherence [3] yet based on our review this remains largely unchanged. Moving forward this issue requires attention to inform protocols for future intervention studies in these populations.

4.1.1 Application of interventions to real world settings

All interventions, regardless of broad groupings, differed by rating levels but remained between pragmatic and equally pragmatic/explanatory on the PRECIS-2 score spectrum, indicating acceptable levels of applicability to real world settings.

Scores were likely due to the fact that almost all studies were rated pragmatic or rather pragmatic for “Eligibility”, Recruitment”, “Setting”, “Outcome” and “Analysis” domains. The most explanatory domains were “organization” and “flexibility in delivery”, due to the varied interventions and their contrast to controls. The varied follow-up periods, and intervention struture are most likely reasons for the lack of trends observed for each intervention type. For example, some peer support interventions required follow-up by home visit and calls more frequently, on more structured formats than others. Other studies required more in-depth, regular supervision and training of peer mentors while others involved once off training and no supervision.

Integration of care interventions displayed on average a more pragmatic score while most of the mhealth interventions fell on the equally pragmatic/explanatory side of the scale, probably due to the organization needed to produce relevant text message content and resources required to deliver the intervention i.e. platform for delivery, mobile phones for patients, literacy, airtime for patients and HCWs. The only interventions rated as explanatory was the cHCT intervention with male involvement, possibly due to its specific recruitment strategy, organization required for issuing invitations, and the level of follow-up employed. Rating results suggest that integration of care, peer support, multicomponent interventions and task shifting may be the most pragmatic interventions to implement.

4.1.2 Duration of intervention effects

Previous reviews [20, 72] noted that there were few interventions exploring retention postpartum period and what did exist was contained to the first 3 months after delivery. This review identified more interventions spanning pregnancy into postpartum as well as only the postpartum period, with most studies assessing intervention effect on retention at 6 months postpartum. Some studies assessed outcomes 6 to 12 months postpartum and others at that time point post-ART initiation. Only 3 studies assessed retention long term, 2 at 18 months and 1 at 24 months indicating these postpartum retention times should be explored further to understand maternal patterns long term. ICC and PCC interventions could also address this period after 24 months to assess maternal patterns of retention and adherence.

4.1.3 Future studies

Based on ongoing studies, examination of interventions to improve retention and ART adherence in pregnant and postpartum women is gaining momentum. This review only identified 33 studies over 3 decades that met our inclusion criteria yet 19 studies over the last few years alone – based on a non-exhaustive search - are now being conducted. This bodes well for identifying more robustly tested interventions over various short and long-term retention periods and adherence measures demonstrating that there will be continued future growth of the evidence described in this review.

4.1.4 Knowledge gaps

Knowledge gaps identified include the absence of ICC and PCC intervention assessments, and is concerning in the light of universal life long ART where women need to remain in care and sustain ART adherence, not just during, but after and in between pregnancies. Examination of long-term ICC and PCC interventions especially, could generate valuable retention and adherence results on which to base implementation and scale-up. Interventions that show promise such as case management require more examination in varied settings as does other interventions only assessed in Sub-Saharan Africa. This is key to allow generalizability of interventions to other contexts. Cost effectiveness of recommended interventions will also be required for varied settings to inform implementation methods, scale-up and sustainability concerns.

4.1.5 Limitations

Review limitations include conducting searches in English, as well as restricting our inclusion criteria to studies with retention or adherence as a primary or secondary outcome which may have led to relevant studies being missed. Although no geographic restrictions were placed and multiple databases searched all but one of included studies was from Sub-Saharan Africa, limiting generalizability of interventions in varied settings. The use of one reviewer for data extraction may have impacted the scientific rigor of this process. Given that successful interventions in one context does not guarantee effectiveness in others with their unique resource availability, behavioural and social variabilities, selection of interventions for adoption and scale up in routine care need to be carefully evaluated. Further the large degree of heterogeneity in intervention type, study design and conduct, outcome measurements and definitions, and duration of follow up precluded the ability to conduct subgroup and a meta-analysis. Studies with small sample sizes may have been inadequately powered.

4.1.6 Conclusions

Although there is evidence that interventions identified, particularly combination interventions, can significantly improve our outcomes of interest, no one intervention demonstrated this absolutely as each intervention type also demonstrated no effect on improving outcomes. Multicomponent interventions, mhealth and integration of services are

highlighted as promising interventions to guide strategies aimed at improving retention in care and ART adherence in pregnant and postpartum women.

Studies with significantly improved, or high non-significant levels of retention, did not persist with time, demonstrated by retention drops with increased length of postpartum, in keeping with the trends described in the literature. Interventions effective to sustain long-term retention are thus needed particularly in the context of universal lifelong ART. This also highlights the gap for ICC and PCC interventions which would address the intermediate period between pregnancies for HIV-positive women. Almost all interventions were scored as pragmatic to implement in real world practice, but the evidence base requires strengthening for outcomes in our populations of interest, which seems a possibility given the number of ongoing studies identified.

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Review & editing: Landon Myer, Nikhat Hoosen

Competing interests

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6 SUPPORTING INFORMATION

S1 Table. Keywords and MeSH Terms used in database searches

Search	Query
#1	Search ((HIV [MeSH Terms]) OR HIV Infections [MeSH Terms]) OR ((HIV OR HIV-1 OR HIV-2 OR HIV1 OR HIV2 OR Human Immunodeficiency Virus OR Human Immunedeficiency Virus OR Human Immune-Deficiency Virus OR Human Immuno-Deficiency Virus OR Acquired Immunodeficiency Syndrome OR Acquired Immunedeficiency Syndrome OR Acquired Immuno-Deficiency Syndrome OR Acquired Immune-Deficiency Syndrome OR Nevirapine OR Zidovudine))
#2	Search ((Antiviral Agents [MeSH Terms]) OR Antiretroviral Therapy, Highly Active [MeSH Terms]) OR ((anti-AIDS OR anti-HIV OR anti HIV OR antiretroviral OR anti-retroviral OR anti retroviral OR HAART))
#3	Search ((((Pregnancy [MeSH Terms]) OR Pregnant Women[MeSH Terms]) OR Postnatal Care[MeSH Terms]) OR Postpartum Period[MeSH Terms] OR Preconception Care[MeSH Terms]) OR ((pregnant OR antenatal OR interconception OR postnatal OR perinatal OR postpartum OR preconception OR prenatal OR mother-to-child OR MTCT OR mother-to-infant OR maternal-infant transmission OR PMTCT))
#4	Search ((((Treatment Adherence and Compliance [MeSH Terms]))) OR Lost to Follow-Up [MeSH Terms]) OR ((adherence OR engagement OR care acceptor OR compliance OR patient acceptance OR retention OR loss to follow up OR lost to follow-up OR lost to follow up OR linkage to care OR pharmacy refill OR self-report OR electronic device monitoring OR plasma drug levels))
#5	#1 AND #2 AND #3 AND #4

S2 Table. Excluded Studies with reasons (n=91)

AUTHOR	YEAR	REASON FOR EXCLUSION
Adeyemo	2013	Case series
Akinde	2019	Interview
Audet	2017	Full paper could not be located
Audet	2018	Protocol
Awiti	2016	Ongoing study
Besada	2016	Interview
Carmone	2014	Incorrect outcome
Cataldo	2017	Qualitative study
Chetty	2018	Author emailed, study results analysis is ongoing
Ciampa	2011	Incorrect outcome
Clouse	2018	Incorrect outcome
Cowan	2015	Protocol
Davey	2012	Incorrect population
Dean	2012	No data
Delva	2010	Therapeutic intervention
DiCarlo	2018	Qualitative study
Drake	2017	Protocol
Ezeanolue	2015	Incorrect population
Fairbanks	2018	Qualitative study
Fayorsey	2016	Duplicate study data
Feinstein	2015	Incorrect population
Finocchario-Kessler	2014	Incorrect population
Finocchario-Kessler	2019	Protocol
Gamell	2017	Incorrect outcome
Geldsetzer	2019	Incorrect population
Gross	2015	Incorrect population
Hanrahan	2019	Incorrect population
Heinemann	2017	Duplicate study data
Jaffer	2016	Dissertation
Joseph Davey	2016	Incorrect population
Kalembo	2013	No intervention
Kassaye	2016	Primary or secondary outcome not relevant
Kebaya	2014	Incorrect population
Kieffer	2015	Ongoing
Kim	2012	No response from author
Liu	2014	Incorrect outcome
Lund	2015	Incorrect population
Mangwiro	2012	Protocol
Masereka	2019	No intervention
Mushamiri	2014	Incorrect population
Napua	2016	No data

Namukwaya		Incomplete data, no author response
"Friends for Life Circles for Option B Plus." *	2015	Ongoing study, reported in S4
"Improving ART Retention and Adherence in Uganda: the WiseMama Study." *	2015	Ongoing study, reported in S4
"Mobile Strategies for Women's and Children's Health: optimizing Adherence and Efficacy of PMTCT/ART." *	2015	Ongoing study, reported in S4
"Postpartum Adherence Clubs to Enhance Support: the PACER Study." *	2015	Duplicate study data
Nct. "Kenya Enhanced Mentor Mother PrograAm (EMMA)." *	2016	Ongoing study, reported in S4
"Postpartum Adherence Clubs for Antiretroviral Therapy." *	2017	Ongoing study, reported in S4
"Support for Perinatal Adherence and Depression." *	2017	Ongoing study, reported in S4
"A Stigma Reduction Intervention at Time of Entry Into Antenatal Care to Improve PMTCT Services in Tanzania	2018	Ongoing study, reported in S4
"Developing and Assessing a Male Engagement Intervention in Option B+ in Malawi." *	2018	Ongoing study, reported in S4
"VITAL Start: brief Facility-based Video Intervention." *	2018	Duplicate study data
"A Peer-Led Intervention to Improve Postpartum Retention in HIV Care." *	2019	Ongoing study, reported in S4
"Adaptation of the Friendship Bench Intervention for HIV-infected Perinatal Women in Lilongwe." *	2019	Ongoing study, reported in S4
"CareConekta: a Smartphone App to Improve Engagement in HIV Care." *	2019	Ongoing study, reported in S4
"Peer Support to Mitigate the Impact of Stigma in Young HIV+ Pregnant & Postpartum Women." *	2019	Ongoing study, reported in S4
"Storytelling to Increase Family Support for Pre Exposure Prophylaxis Use." *	2019	Incorrect population, included HIV negative women
Odayar	2019	Protocol
Odeny	2018	Protocol
Oyeledun	2014	Protocol
Pellowski	2019	Review
Peltzer	2017	No response from author
Pfeiffer	2017	No response from author
Phillips	2019	No intervention
Potter	2019	Incorrect outcome
Puchalski Ritchie	2019	Review
Reimers	2018	Incorrect population
Reimers	2016	Protocol
Reynolds	2016	Incorrect population
Rosenberg	2015	Incorrect outcome
Rosenberg	2014	Protocol

Rotheram-Borus	2011	Protocol
Rotheram-Borus	2014	Data not provided from author
Sam-Agudu	2017	Protocol
Sando	2014	Protocol
Shroufi	2013	No data
Stein	2017	Ongoing reported in S4
Toro	2012	Review
Uwimana	2013	Incorrect population
van Lettow	2014	No intervention
van Lettow	2019	No response from author
Wagner	2019	Protocol
Wanga	2019	No data
Watt	2019	Protocol
Weiss	2014	Incorrect outcome
Wesevich	2020	Incorrect outcome
Williams	2014	Cannot locate
Woelk	2016	Protocol
Wong	2006	Incorrect population
Yotebieng	2017	Protocol
Yotebieng	2016	Duplicate study data
Zunza	2017	Incorrect outcome
Zuyderduin	2009	Incorrect population

* No primary authors listed in search results since this is still ongoing

S3 Table. Ongoing RCTs (n=19) identified not included in this review

Trial name	Year	Country	Primary/ secondary outcomes	Retention/adherence assessmen timepoints	Intervention	Control
CareConekta: A Smartphone App to Improve Engagement in HIV Care	2019	South Africa	Retention and viral suppression	6 months after delivery	CareConekta smartphone application enrolling pregnant women, plus text notifications mobility tracking, opt-in to phone calls, WhatsApp messages, advice on medication supply and nearby facilities when travelling	Standard CareConekta, tracking mobility with no additional features.
A Stigma Reduction Intervention at Time of Entry Into Antenatal Care to Improve PMTCT Services in Tanzania	2018	Tanzania	engagement in care, ART adherence	3 months after enrollment	Video and brief counselling addressing HIV stigma at ANC, stigma-based counselling sessions for HIV+ women, building on video content.	SOC
Mobile Strategies for Women's and Children's Health: Optimizing Adherence and Efficacy of PMTCT/ART (Mobile WAChx)	2015	Kenya	Retention and adherence	2 years postpartum	unidirectional SMS vs. bidirectional text messaging between participant and provider for pregnant HIV+ women	no SMS
Cluster randomised trial to evaluate an intervention for depressed HIV-positive women in the perinatal period, to enhance child development and reduce maternal depression	2017	South Africa	Adherence	Over entire trial period	combined behavioural activation and parenting programme, with sessions during pregnancy and following delivery, home-based counselling by lay counsellors	Limited number ANC and postnatal support calls
Improving early ANC attendance through community engagement and dialogue: project ACCLAIM in three African countries	2015	Swaziland, Uganda, Zimbabwe	retention	6-8 weeks after birth	community leader engagement, Community Days and dialogues, male and female MCH classes led by peer facilitators for pregnant and postpartum women	SOC
Friends for Life Circles for Option B Plus (FLCs)	2016	Uganda	Retention and Adherence	2 years postpartum	peer support groups of eight to ten women in the community with income generating activities to improve maternal adherence to clinic appointments and ART	SOC
Improving ART Retention and Adherence in Uganda: The WiseMama Study	2015	Uganda	adherence	6 and 9 months	electronic pill container for ARVs, failure to open container within 60 minutes of dose time, triggers text message reminder + monthly counselling sessions	SOC
Kenya Enhanced Mentor Mother ProgrAm (EMMA)	2016	Kenya	adherence and retention	72 weeks postpartum	SOC plus study-specific enhanced care interventions from the clinic's Mentor Mothers.	SOC for PMCT from clinic's Mentor Mothers
Support for Perinatal Adherence and Depression	2017	South Africa	adherence	3 months postpartum	INSPireD: 5-8 session group intervention, to decrease depressive symptoms and improve adherence among HIV-infected pregnant and postpartum women.	SOC counseling services, start intervention when first experimental group is complete

Postpartum Adherence Clubs for Antiretroviral Therapy (PACART)	2017	South Africa	Viral suppression and retention	2 years	Adherence clubs community health workers provide health education, weigh participants, ask about symptoms, and dispense pre-packed ART.	SOC
Developing and Assessing a Male Engagement Intervention in Option B+ in Malawi	2018	Malawi	retention and viral suppression	1 year	Enhanced Couple HIV Testing and Counseling, study-specific partner referral cards to encourage male partners to attend ANC. Those not presenting receive three enhanced couple counselling sessions	SOC
Adaptation of the Friendship Bench Intervention for HIV-infected Perinatal Women in Lilongwe	2019	Malawi	retention	6 months	problem solving therapy- based ART adherence support, individual prenatal and group postnatal counselling sessions. Women bring a person of their choice as social support to manage HIV and/or depression, assist women with medication collection during late pregnancy/postpartum, trained psychosocial counselor will conduct home visits	SOC mental health in public facilities in Malawi
Peer Support to Mitigate the Impact of Stigma in Young HIV+ Pregnant & Postpartum Women	2019	South Africa	Retention and viral suppression	6 months	monthly peer support groups during pregnancy and postpartum, separate from routine health services, facilitated by WLHIV and experience of PMTCT services	SOC
A Peer-Led Intervention to Improve Postpartum Retention in HIV Care	2019	USA	Retention and Viral Suppression	1 year postpartum	prenatal sessions and postpartum sessions with peer facilitator, consisting of structured educational content followed by unstructured conversation	Prenatal/postpartum sessions with peer facilitator on parenting and baby care
Mother and Infant Visit Adherence and Treatment Engagement Study (MOTIVATE!)	2015	Kenya	adherence and retention	1 year postpartum	Home visits from community mentor mothers to assist with safe disclosure, safe infant feeding, safer sex , family planning, encourage early infant testing, promote ART adherence and return for HIV care visits + text messages	SOC
Maternal depression treatment in HIV (M-DEPTH) Study	2019	Uganda	viral suppression, adherence and retention	1 month postpartum and through study period	Task-shifted depression screening and psychoeducation, depression diagnosis, and evidence-based problem solving therapy or antidepressant therapy implemented by trained peer mothers and midwife nurses in addition to usual care.	referrals to mental health specialists, MOH program providing psychosocial support/ education for pregnancy management/ PMTCT adherence
Long Term Outcomes of Therapy in Women Initiated on Lifelong ART Because of Pregnancy in DR Congo	2017	DRC	LTFU and Virological suppression	delivery, six weeks, 12 and 24 weeks postpartum	CQI initiatives implemented at facility level using participatory data-driven approaches and on-site monitoring and supervisory support	SOC + strengthening of the data collection system
Evaluation of the Impact of Mobile Phone Messages on ART and PMTCT Adherence in Mozambique (SMSaude)	2013	Mozambique	Retention	1 year	SMS reminders to PMTCT cohort experimental group	no SMS reminders
Management and Optimization of Nutrition, Antenatal, Reproductive, Child Health & HIV Care (MONARCH)	2017	South Africa	retention	6 weeks postpartum	Quality improvement of clinic processes for maternal and child health	SOC

PART C APPENDICES

Appendix A: PRISMA 2009 Checklist for manuscript

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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 - 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
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.	5
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Table
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).	5
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 - 6

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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
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.	6

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).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6 - 7
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.	7 - 9
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.	9 – 27,
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).	27 - 29
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.	17 - 19, 25 – 27, Table 2 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	27 - 29
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	29 - 32
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).	33 -39
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).	39
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	39- 40
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.	40

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. doi:10.1371/journal.pmed1000097

APPENDIX B: Submission Guidelines for Authors – PLOS One

Style and Format

File format	Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected. LaTeX manuscripts must be submitted as PDFs. Read the LaTeX guidelines.
Length	Manuscripts can be any length. There are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout and spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page and line numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English. You may submit translations of the manuscript or abstract as supporting information. Read the supporting information guidelines.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference style	PLOS uses "Vancouver" style, as outlined in the ICMJE sample references. See reference formatting examples and additional instructions below.
Equations	We recommend using MathType for display and inline equations, as it will provide the most reliable outcome. If this is not possible, Equation Editor or Microsoft's Insert→Equation function is acceptable. Avoid using MathType, Equation Editor, or the Insert→Equation function to insert single variables (e.g., "$a^2 + b^2 = c^2$"), Greek or other symbols (e.g., β, Δ, or ′ [prime]), or mathematical operators (e.g., x, ≥, or ±) in running text. Wherever possible, insert single symbols as normal text with the correct Unicode (hex) values. Do not use MathType, Equation Editor, or the Insert→Equation function for only a portion of an equation. Rather, ensure that the entire equation is included. Equations should not contain a mix of different equation tools. Avoid "hybrid" inline or display equations, in which part is text and part is MathType, or part is MathType and part is Equation Editor.

Nomenclature	Use correct and established nomenclature wherever possible.	
	Units of measurement	Use SI units. If you do not use these exclusively, provide the SI value in parentheses after each value. Read more about SI units.
	Drugs	Provide the Recommended International Non-Proprietary Name (rINN).
	Species names	Write in italics (e.g., *Homo sapiens*). Write out in full the genus and species, both in the title of the manuscript and at the first mention of an organism in a paper. After first mention, the first letter of the genus name followed by the full species name may be used (e.g., *H. sapiens*).
	Genes, mutations, genotypes, and alleles	Write in italics. Use the recommended name by consulting the appropriate genetic nomenclature database (e.g., HGNC for human genes; we strongly recommend using this tool to check against previously approved names). It is sometimes advisable to indicate the synonyms for the gene the first time it appears in the text. Gene prefixes such as those used for oncogenes or cellular localization should be shown in roman typeface (e.g., v-fes, c-MYC).
	Allergens	The systematic allergen nomenclature of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-committee should be used for manuscripts that include the description or use of allergenic proteins. For manuscripts describing new allergens, the systematic name of the allergen should be approved by the WHO/IUIS Allergen Nomenclature Sub-Committee prior to manuscript publication. Examples of the systematic allergen nomenclature can be found at the WHO/IUIS Allergen Nomenclature site.

Manuscript Organization

Manuscripts should be organized as follows. Instructions for each element appear below the list.

Beginning section	*The following elements are required, in order:* › Title page: List title, authors, and affiliations as first page of manuscript › Abstract › Introduction
Middle section	*The following elements can be renamed as needed and presented in any order:* › Materials and Methods › Results › Discussion › Conclusions (optional)
Ending section	*The following elements are required, in order:* › Acknowledgments › References › Supporting information captions (if applicable)
Other elements	› Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. › Tables are inserted immediately after the first paragraph in which they are cited. › Supporting information files are uploaded separately.

Systematic reviews and meta-analyses

A systematic review paper, as defined by The Cochrane Collaboration, is a review of a clearly formulated question that uses explicit, systematic methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. These reviews differ substantially from narrative-based reviews or synthesis articles. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.

Reports of systematic reviews and meta-analyses must include a completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist and flow diagram to accompany the main text. Blank templates are available here:

- Checklist: PDF or Word document
- Flow diagram: PDF or Word document

Authors must also state in their "Methods" section whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as supporting information and provide the registry number in the abstract.

If your article is a systematic review or a meta-analysis you should:

- State this in your cover letter
- Select "Research Article" as your article type when submitting
- Include the PRISMA flow diagram as Fig 1 (required where applicable)
- Include the PRISMA checklist as supporting information