

ORIGINAL ARTICLE

Adverse perinatal outcomes associated with timing of initiation of antiretroviral therapy: Systematic review and meta-analysis

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Abstract

Background: The World Health Organization (WHO) recommends immediate initiation of lifelong antiretroviral therapy (ART) for all people living with HIV, including pregnant women. As a result, an increasing number of women living with HIV conceive while taking ART, the vast majority of whom reside in low- and middle-income countries (LMICs). We aimed to assess the association between timing of ART initiation and perinatal outcomes.

Methods: We conducted a systematic literature review by searching PubMed, CINAHL (EBSCOhost), Global Health (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials and four clinical trial databases (WHO International Clinical Trials Registry Platform, the Pan African Clinical Trials Registry, the [ClinicalTrials.gov](https://clinicaltrials.gov) database, and the ISRCTN Registry) from 1 January 1980 to 28 April 2018. We identified studies reporting specific perinatal outcomes among pregnant women living with HIV according to timing of ART initiation and extracted data. Perinatal outcomes assessed were preterm birth (<37 weeks), very preterm birth (<32 weeks), low birthweight (<2500 g), very low birthweight (<1500 g), small for gestational age (<10th centile), very small for gestational age (<3rd centile) and neonatal death (<29 days). Random-effects meta-analyses examined perinatal outcomes associated with preconception and antenatal ART initiation as well as according to trimesters of antenatal initiation. We performed quality assessments and subgroup and sensitivity analyses, and assessed the effect of adjustment for confounders. This systematic review and meta-analyses is registered with PROSPERO, number CRD42021248987.

Results: Of 51 874 unique citations, 25 studies (eight prospective and 17 retrospective cohort studies) were eligible for analysis, including 40 920 women living with HIV. Preconception ART initiation was associated with a significantly increased risk of preterm birth (relative risk 1.16; 95% confidence interval

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[CI] 1.03–1.31) compared with antenatal ART initiation. Preconception ART initiation was not significantly associated with very preterm birth, low birthweight, very low birthweight, small for gestational age, very small for gestational age, or neonatal death. First trimester exposure (i.e. preconception or first trimester initiation) was not significantly associated with any increased risk of adverse perinatal outcomes. No significant association between timing of ART initiation and adverse perinatal outcomes was found in the studies of higher quality and those conducted in LMICs.

Conclusion: Preconception ART initiation is associated with preterm birth but no other adverse perinatal outcomes. In LMICs, where most pregnant women living with HIV reside, the timing of ART initiation was not associated with any adverse perinatal outcomes.

KEYWORDS

antiretroviral therapy, HIV, low birthweight, neonatal death, preterm birth, small for gestational age

INTRODUCTION

Of the 38.0 million people currently living with HIV, 15.5 million are women aged 15–49 years, of whom 1.3 million are pregnant each year [1]. The vast majority of pregnant women living with HIV reside in low- and middle-income countries (LMICs). In 2013, the World Health Organization (WHO) recommended that all pregnant women living with HIV should receive antiretroviral therapy (ART) to prevent vertical transmission of HIV [2]. This led to an increase in the global proportion of pregnant women living with HIV who received ART during pregnancy, from 44% in 2010 to 82% in 2018, resulting in a 41% reduction in vertical HIV transmission in the same period [1]. In 2015, the WHO adopted a ‘treat all’ approach, which recommended that all people living with HIV, including pregnant women, should initiate lifelong ART as soon as possible after diagnosis [3]. This resulted in a dramatic increase in the proportion of pregnant women living with HIV who received ART at the time of conception, from 7% in 2010 to 51% in 2018, in the 23 focus countries in which 86% of global pregnant women living with HIV reside [4]. Preconception ART has been linked to extremely low rates of vertical transmission of HIV [5, 6] while also improving maternal health. Despite this, ART during pregnancy has potential adverse effects.

LMICs carry the highest burden of neonatal and child mortality [7]. Preterm birth is the most important cause of neonatal and child mortality globally [8], with an estimated 14.8 million babies born preterm each year [9]. Furthermore, 23.3 million small for gestational age

babies born each year account for 21.9% of neonatal deaths in LMICs [10]. Preterm birth and small for gestational age are both causes of low birthweight (18 million/year), an outcome measure frequently used in LMICs as gestational age at birth is often unknown [11]. United Nations Sustainable Development Goal 3 target 3.2 aims to reduce preventable deaths of newborns and children aged <5 years [12], a goal that will be difficult to achieve without improving the perinatal outcomes that are the basis of many of these deaths.

Pregnant ART-naïve women living with HIV are associated with increased risk of preterm birth (relative risk [RR] 1.50; 95% confidence interval [CI] 1.24–1.82), low birthweight (RR 1.62; 95% CI 1.41–1.86), small for gestational age (RR 1.31; 95% CI 1.14–1.51), and stillbirth (RR 1.67; 95% CI 1.05–2.66) [13]. ART in pregnancy has also been linked to increased rates of adverse perinatal outcomes, although studies have shown conflicting results related to regimen complexity (e.g. zidovudine monotherapy vs. ART, i.e. triple drug therapy) and type of regimen/class of drugs (e.g. protease inhibitors [PIs]) [14, 15]. Some studies have shown an increased risk of preterm birth with antenatal initiation of ART compared with zidovudine monotherapy [16, 17], but this was not seen in other studies [18, 19]. Similarly, PI-based ART was associated with an increased risk of preterm birth in a number of studies [20, 21] but not in others [22]. A recent network meta-analysis of randomized controlled trials (RCTs) of ART initiated during pregnancy found that PI lopinavir/ritonavir-containing regimens were associated with the highest risks of adverse perinatal outcomes [23].

A key outstanding question is whether the timing of ART initiation impacts perinatal outcomes in pregnant women living with HIV. We conducted a systematic review and meta-analysis of studies reporting the association of adverse perinatal outcomes with preconception and antenatal ART initiation as well as according to trimesters of antenatal initiation.

METHODS

Search strategy

The systematic review and meta-analysis were conducted according to a protocol developed based on the Cochrane guidelines [24]. We searched PubMed, CINAHL (EBSCOhost), Global Health (Ovid), EMBASE (Ovid), and the Cochrane Central Register of Controlled Trials for studies published between 1 January 1980 and 28 April 2018. We also searched four clinical trial databases (WHO International Clinical Trials Registry Platform, the Pan African Clinical Trials Registry, the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database, and the ISRCTN Registry). Free text and controlled vocabulary search terms for “adverse perinatal outcomes”, “HIV” and “antiretroviral therapy” were used, with both full-text articles and abstracts considered. For full search terms see Appendix 1. No methodological or language restrictions were applied. Retrieved articles were imported into EndNote X7 reference manager (Clarivate Analytics, Philadelphia, Pennsylvania, USA) and de-duplicated.

Eligibility criteria

Studies were eligible if they contained information on the association of timing of ART initiation with predefined adverse perinatal outcomes. Categories of timing of ART initiation were preconception, antenatal, first trimester, second trimester and third trimester, as defined in individual studies (Appendix 3.2). ART was defined as triple drug antiretroviral therapy. Inclusion criteria were study design (RCTs, prospective and retrospective cohort studies, case-control studies), study population (pregnant women living with HIV), exposure (ART), comparator (ART initiated at a different time), and perinatal outcomes defined as follows: preterm birth ($<37^{+0}$ weeks' gestation) [25]; very preterm birth ($<32^{+0}$ weeks' gestation) [25]; low birthweight (<2500 g) [11]; very low birthweight (<1500 g) [11]; small for gestational age (birthweight for gestational age $<10^{\text{th}}$ centile of the reference chart used at the study site) [26]; very small for gestational age (birthweight for gestational age $<3^{\text{rd}}$ centile) [26]; and neonatal death (infant death in first 28 days of life) [27].

Study selection and data extraction

The titles and abstracts of studies retrieved by the literature search were screened by at least two independent investigators (HS, MK, ZB, and CS) to identify potentially relevant articles. Full-text articles of relevant citations were retrieved and assessed against the eligibility criteria. The reference lists of included studies were assessed for additional relevant citations. The uniqueness of each included study was assessed and, where a cohort was reported more than once, the manuscript containing the most recent and complete data was retained. Conversely, where multiple manuscripts reported different outcomes for the same cohort, each was included.

Once the eligible studies were selected, data on study characteristics, populations, ART exposures, and perinatal outcomes were independently extracted by at least two investigators (HS, MK, ZB, and CS). Perinatal outcome data were collected, and unadjusted and adjusted RRs and odds ratios (ORs) and 95% CIs were extracted. In addition, detailed information was extracted regarding methods used to adjust for confounders, including regression analysis (i.e. confounders corrected for), risk factor analysis (i.e. risk factors not significantly different between groups), and matching (Appendix 2.5–2.6). Any ambiguities or disagreements were resolved through discussion with the senior investigator (JH).

Quality Assessment

The quality of individual cohort studies was independently assessed by at least two investigators (HS, MK, ZB, and CS) using an adapted version of the Newcastle–Ottawa Scale [28] assessing three domains: Selection of participants (maximum 4 points); comparability of participants and correction for confounding factors (maximum 2 points); outcome assessments (maximum 3 points) [13]. Studies were classified as poor, average, or good quality according to predefined criteria (Appendix 2.1–2.4).

Statistical analysis

RRs and corresponding 95% CIs were used as the primary measure to assess the association between the timing of ART initiation and perinatal outcomes. Dichotomous unadjusted outcome data according to timing of ART initiation were used to generate RRs, irrespective of study quality. Pairwise meta-analysis was carried out if two or more studies reported the same perinatal outcome for the same comparison of timings of ART initiation. For all meta-analyses, a random-effects model was used to

calculate a weighted summary effect estimate and 95% CI. Meta-analyses were represented in forest plots, and the I^2 statistic was used to quantify heterogeneity due to clinical and methodological variability. The degree of heterogeneity was interpreted as none (<25%), low (25%–49%), moderate (50%–74%), or high ($\geq 75\%$). Pre-specified subgroup analyses were performed to assess the effect of covariates (i.e. country income status, study quality, and class of ART) on associations between timing of ART initiation and perinatal outcomes. Sensitivity analyses were conducted to assess the effect of studies with large effect sizes, studies that included twins, and adjustment for confounders. Peters' test was used to assess publication bias in meta-analyses containing a minimum of 10 studies. All statistical analyses were carried out with Stata version 13, and the systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. The protocol is registered online with PROSPERO, number CRD42021248987.

RESULTS

Our search yielded 51 874 unique citations, of which 25 studies reporting on timing of ART initiation and perinatal outcomes were included in the meta-analysis (Figure 1). The perinatal outcomes reported were preterm birth (18 studies), very preterm birth (six), low birthweight (11), very low birthweight (four), small for gestational age (12), very small for gestational age (three), and neonatal death (two) (Figure 1). The studies, countries, country income status, recruitment periods, number of women

analysed, population characteristics, methods to estimate gestational age and correct for confounding, and quality assessments are summarized in Table 1 [6, 16, 18, 30–51].

Eight (32%) prospective and 17 (68%) retrospective cohort studies analysed data from 40 920 pregnancies in 15 countries (Table 1). No relevant RCTs or case-control studies were found. The included studies were published between 2003 and 2018, and patients were recruited during 1984–2016 (Table 1). In total, 12 studies (48%) with 19 582 women took place in high-income countries (HICs), and 13 studies (52%) with 21 338 women took place in LMICs.

A total of 16 (64%) studies reported the methods used to determine gestational age, with only one study using first trimester ultrasound [37], which is the most accurate method of establishing gestational age [52]. In total, 11 (44%) studies used methods to adjust for confounding factors (Table 1). Regression analysis was conducted in nine studies, whereas risk factor analysis was conducted in three studies (Appendix 2.5–2.6). In the 16 comparisons that were adjusted for covariates in individual studies, only three resulted in a change in the significance of the effect estimate (Appendix 7). Quality assessments rated 18 studies (72%) as poor quality, seven (28%) as average quality, and none as good quality (Table 1, Appendix 2.3–2.4).

For each included study, the type of ART and comparisons of timings of ART initiation, along with perinatal outcomes analysed, are displayed in Table 2. In total, 24 (96%) studies compared preconception and antenatal ART initiation, seven (28%) studies compared different trimesters of antenatal ART initiation, and six (24%) studies compared both preconception and antenatal trimesters

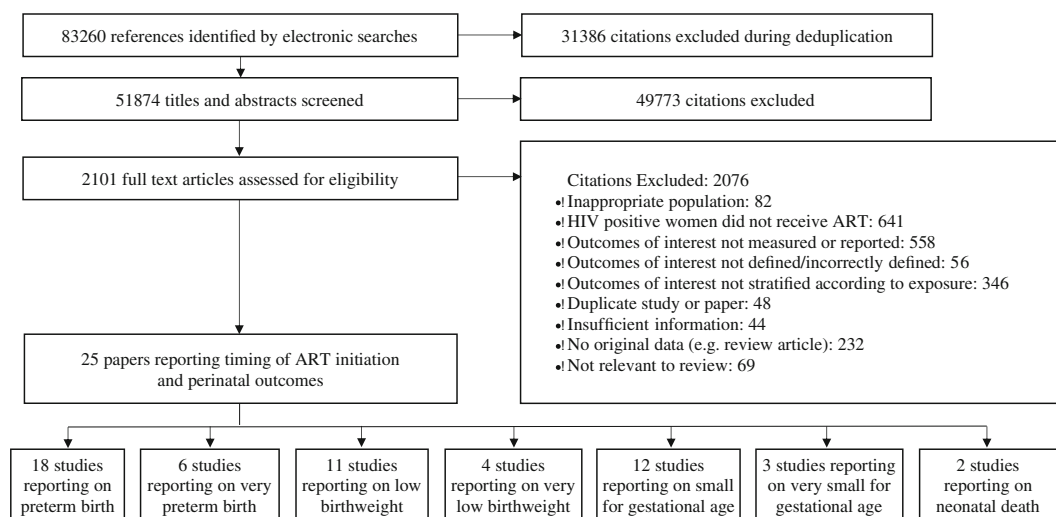


FIGURE 1 Flow diagram of study selection process. See Methods for definitions of perinatal outcomes. Abbreviations: ART, antiretroviral therapy. 'Inappropriate population' included women living with HIV who were not pregnant, 'not relevant to review' included assisted reproductive technology, and 'insufficient information' means the paper did not provide relevant data.

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis

Study	Country	Country income	Recruitment period	Number of women analysed	Population characteristics	Methods to correct for confounders	Gestational age estimation method	Quality assessment
Prospective cohorts								
Aaron (2012)[30]	USA	High	1/2000 to 1/2011	183	First-born twin included, 38.3% smoking, 18.0% IDU, urban setting	Regression analysis	LNMP confirmed by second trimester ultrasound	Average
Ekouevi (2008)[34]	Ivory Coast	Low/middle	3/2001 to 8/2007	139	Twins excluded, recruited from antenatal clinics, urban setting	None	Symphysis fundal height	Poor
Kowalska (2003)[36]	Poland	High	1/1995 to 2/2003	40	Twins included, 47.1% IDU, recruited from an outpatient HIV clinic	None	LNMP	Poor
Li (2016)[18]	Tanzania	Low/middle	11/2004 to 10/2011	1094	Recruited from hospitals, health centres, and dispensaries, urban setting	None	LNMP	Poor
Machado (2009)[38]	Brazil	Low/middle	1996 to 2006	304	Twins excluded, 5.4% alcohol use, 21.3% smoking, 9.0% IDU, recruited from an HIV reference centre, urban setting	Regression analysis and risk factor analysis	LNMP or ultrasound	Poor
Malaba (2017)[39]	South Africa	Low/middle	4/2013 to 8/2015	1554	Twins excluded, recruited from large community primary care facility, urban setting	Regression analysis	LNMP	Average
Rudin 2011[44]	Switzerland	High	1984 to 2007	418	Twins excluded, 22% smoking, 26% IDU	None	No description	Poor
Townsend 2007[49]	United Kingdom and Ireland	High	1990 to 2005	2201	Singleton pregnancies, 5.0% IDU	Regression analysis	No description	Poor
Retrospective cohorts								
Anji (2013)[31]	South Africa	Low/middle	1/10/2007 to 31/3/2009	245	Twins excluded, alcohol, smoking and IDU was negligible, all tertiary hospital deliveries	None	Late ultrasound	Poor

(Continues)

TABLE 1 (Continued)

Study	Country	Country income	Recruitment period	Number of women analysed	Population characteristics	Methods to correct for confounders	Gestational age estimation method	Quality assessment
Chagomerana (2017)[32]	Malawi	Low/middle	1/4/2012 to 15/11/2015	2909	Twins excluded, all women delivered in a secondary hospital	Regression analysis	LNMP	Average
Chen (2012)[16]	Botswana	Low/middle	1/5/2009 to 30/4/2011	3081	First-born twin included, 5.3% alcohol use, 1.7% smoking, all hospital deliveries	Regression analysis	LNMP, symphysis-fundal height or ultrasound	Average
Chetty (2018)[33]	South Africa	Low/middle	2010 to 2015	2021	Alcohol, smoking and IDU under 10%. Enrolment clinic: 56.6% rural, 41.9% preurban	None	LNMP, symphysis-fundal height or ultrasound	Poor
Favarato (2018)[35]	United Kingdom and Ireland	High	2007 to 2015	6073	Twins excluded, 1.7% IDU	Regression analysis	No description	Poor
Lopez (2014)[37]	Spain	High	1/2006 to 12/2011	149	Twins excluded, 31.4% smoking, 6.4% IDU, recruited in a tertiary hospital, urban setting	Risk factor analysis	First trimester ultrasound	Average
Mandelbrot (2015)[6]	France	High	2000 to 2011	8678	Twins included, women recruited from 90 perinatal centres, all hospital deliveries	None	LNMP and/or ultrasound	Poor
Montgomery-Taylor (2015)[40]	United Kingdom	High	1/2008 to 12/2012	61	13.0% alcohol use, 3.0% smoking, recruited in a tertiary hospital, urban setting, all hospital deliveries	None	No description	Poor
Oomeer (2015)[41]	United Kingdom	High	2007 to 2014	37	Twins included	None	No description	Poor
Ramokolo 2017[42]	South Africa	Low/middle	10/2012 to 5/2013	1396	Recruited from primary health facilities	Regression analysis	LNMP	Poor

TABLE 1 (Continued)

Study	Country	Country income	Recruitment period	Number of women analysed	Population characteristics	Methods to correct for confounders	Gestational age estimation method	Quality assessment
Rempis (2017)[43]	Uganda	Low/middle	2/2013 to 12/2013	94	Twins excluded, all delivered in a private referral hospital	None	No description	Poor
Samuel (2014)[45]	United Kingdom	High	1/3/2004 to 1/12/2010	99	Twins excluded, 3.4% IDU, recruited from HIV specialist centres, urban setting	None	No description	Poor
Sebitloane (2017)[46]	South Africa	Low/middle	1/4/2011 to 30/4/2014	725	Twins excluded, women recruited and delivered at a regional hospital, urban setting	None	No description	Poor
Short (2014)[47]	United Kingdom	High	1999 to 2010	251	Twins included, 13.0% smoking, recruited from an HIV antenatal clinic, all deliveries in a tertiary hospital, urban setting	None	No description	Poor
Snijdwind (2018)[48]	Netherlands	High	1/1997 to 2/2015	1392	Twins included, 6.1% alcohol use, 8.2% smoking, 1.7% IDU	Risk factor analysis	LNMP or early ultrasound	Average
Zash (2016)[51]	Botswana	Low/middle	5/2009 to 4/2011 and 4/2013 to 4/2014	4392	Twins included, recruitment and delivery at the two largest public maternity wards in the country, all hospital deliveries	None	LNMP	Poor
Zash (2018)[50]	Botswana	Low/middle	3/2013 to 8/2016	3384	Twins excluded, 8.8% alcohol consumption or smoking	Regression analysis	LNMP confirmed by ultrasound where possible	Average

Abbreviations: IDU, intravenous drug user; LNMP, last normal menstrual period.

TABLE 2 Antiretroviral therapies, timing of ART initiation and perinatal outcomes reported by studies included in the meta-analysis

Study	ART	Preconception versus antenatal	Preconception/ T1 versus T2/T3	T1 versus T2	T2 versus T3	T1 versus T3	Outcome
Prospective cohorts							
Aaron (2012)[30]	63.9% PI-based ART 21.3% NNRTI-based ART 14.8% NRTI-based ART	Yes	Yes	Yes	Yes	Yes	Small for gestational age, very small for gestational age
Ekouevi (2008)[34]	100% NNRTI-based ART	Yes	No	No	No	No	Low birthweight
Kowalska (2003)[36]	60.9% non-PI-based ART 39.1% PI-based ART	Yes	Yes	Yes	Yes	Yes	Preterm birth
Li (2016)[18]	94.0% NNRTI-based ART 4.5% not reported 1.5% PI-based ART	Yes	No	No	No	No	Preterm birth, low birthweight, small for gestational age, very small for gestational age
Machado (2009)[38]	68.1% PI-based ART 31.9% NNRTI-based ART	Yes	No	No	No	No	Preterm birth, low birthweight
Malaba (2017)[39]	97.4% NNRTI-based ART 2.6% PI-based ART	Yes	Yes	Yes	Yes	Yes	Preterm birth, very preterm birth, low birthweight, very low birthweight, small for gestational age
Rudin 2011[44]	84.0% PI-based ART 16.0% non-PI-based ART	Yes	No	No	No	No	Preterm birth
Townsend 2007[49]	54.1% NNRTI-based ART 37.1% PI-based ART 6.7% ART with PI + NNRTI 2% NRTI-based ART	No	Yes	No	No	No	Preterm birth
Retrospective cohorts							
Aniji (2013)[31]	95.5% NNRTI-based ART 4.5% PI-based ART	Yes	No	No	No	No	Low birthweight, very low birthweight
Chagomerana (2017)[32]	100% NNRTI-based ART	Yes	Yes	Yes	No	No	Preterm birth, very preterm birth
Chen (2012)[16]	90.1% NNRTI-based ART 9.9% PI-based ART	Yes	No	No	No	No	Preterm birth, small for gestational age, neonatal death
Chetty (2018)[33]	100% NNRTI-based ART	Yes	No	No	No	No	Preterm birth, very preterm birth, low birthweight, small for gestational age
Favarato (2018)[35]	69.0% PI-based ART 31.0% NNRTI-based ART	Yes	No	No	No	No	Preterm birth
Lopez (2014)[37]	67.9% PI-based ART 32.1% NNRTI-based ART	Yes	No	No	No	No	Small for gestational age

TABLE 2 (Continued)

Study	ART	Preconception versus antenatal	Preconception/ T1 versus T2/T3	T1 versus T2	T2 versus T3	T1 versus T3	Outcome
Mandelbrot (2015)[6]	76.0% PI-based ART 15.8% NNRTI-based ART 5.9% NRTI-based ART	Yes	Yes	Yes	Yes	Yes	Preterm birth, very preterm birth
Montgomery-Taylor (2015)[40]	55.9% PI-based ART 37.2% NNRTI-based ART 6.9% other ART	Yes	No	No	No	No	Small for gestational age
Oomeer (2015)[41]	100% PI-based ART	Yes	No	No	No	No	Low birthweight
Ramokolo 2017[42]	100% NNRTI-based ART	Yes	No	No	No	No	Preterm birth, low birthweight, small for gestational age
Rempis (2017)[43]	100% NNRTI-based ART	Yes	No	No	No	No	Small for gestational age
Samuel (2014)[45]	100% PI-based ART	Yes	No	No	No	No	Preterm birth, low birthweight
Sebitloane (2017)[46]	100% NNRTI-based ART	Yes	No	No	No	No	Preterm birth
Short (2014)[47]	57.6% NNRTI-based ART 40.3% PI-based ART 2.1% NRTI-based ART	Yes	No	No	No	No	Preterm birth
Snijdwind (2018) [48]	66.7% PI-based ART 31.5% NNRTI-based ART 0.9% PI+NNRTI or NRTI-based ART	Yes	No	No	No	No	Preterm birth, very preterm birth, low birthweight, very low birthweight, small for gestational age
Zash (2016)[51]	37.0% TDF/FTC/EFV 63.0% other ART	Yes	No	No	No	No	Preterm birth, small for gestational age
Zash (2018)[50]	100% NNRTI-based ART	Yes	Yes	Yes	No	No	Preterm birth, very preterm birth, low birthweight, very low birthweight, small for gestational age, very small for gestational age, neonatal death

Notes: ARTs are given for each study as a whole. Detailed information on ART regimens according to timing of ART initiation is presented in Appendix 3.1. If ART regimens differed by timing of ART initiation arm in individual studies, then the proportions of ART regimens in each arm were weighed according to the number of people in each arm. Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; FTC, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir; T1, first trimester; T2, second trimester; T3, third trimester.

(Table 2). Only four studies had uniform ART regimens for all timing of ART initiation categories [41, 43, 45, 50]. In all remaining studies, either mixtures of regimens were used across the different ART initiation categories or details were only given for the regimen(s) used in the study as a whole (Appendix 3.1).

We conducted random-effects meta-analyses to compare perinatal outcomes in relation to different timings of ART initiation and presented these in forest plots (Figure 2, Table 3, Appendix 4.1–4.5). Subgroups of studies conducted in HICs and LMICs were analysed, as were subgroups of poor- and average-quality studies, and

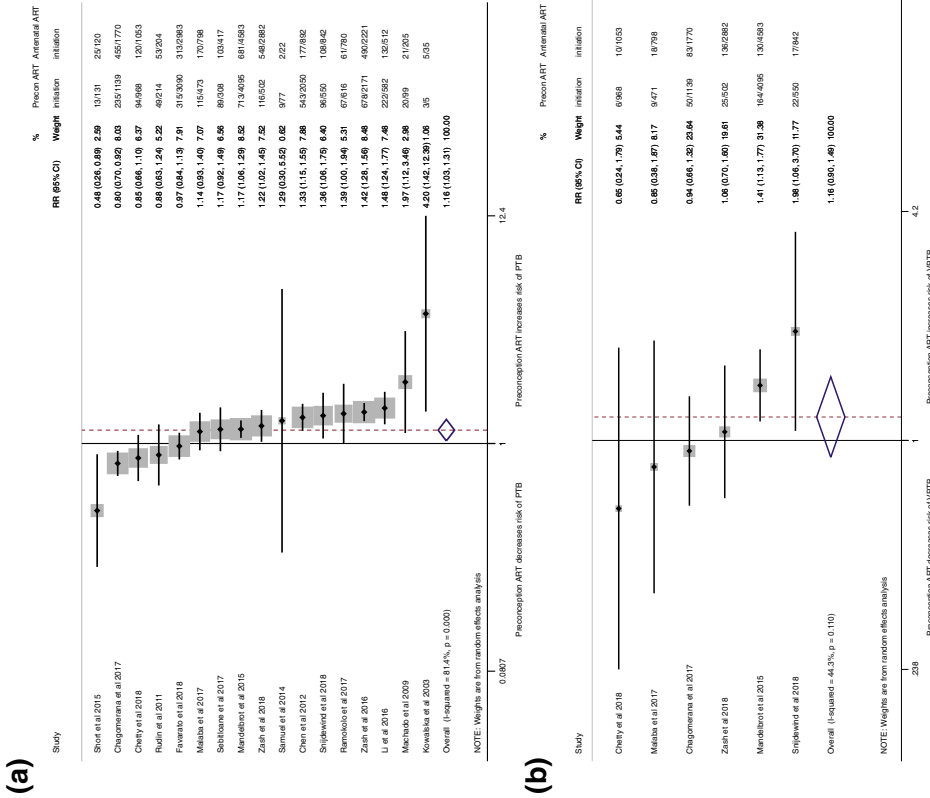
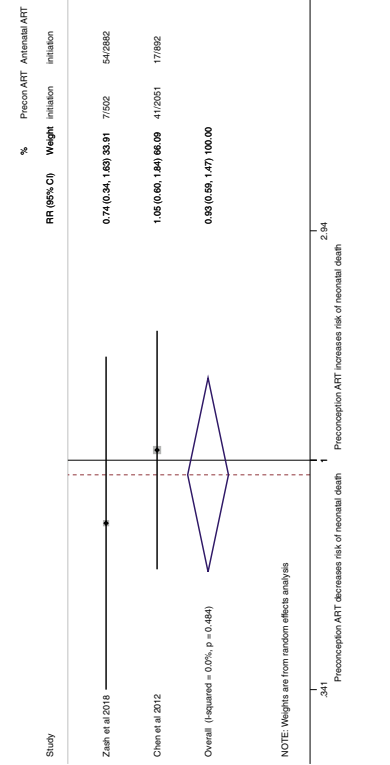
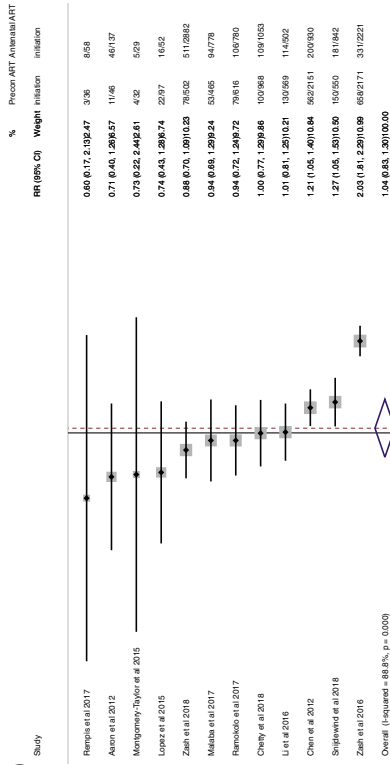


FIGURE 2 Random-effects meta-analyses of risk of perinatal outcomes associated with preconception ART initiation compared with antenatal ART initiation. Forest plots depicting RR and 95% CI of random-effects meta-analyses of perinatal outcomes associated with preconception compared with antenatal ART initiation. Perinatal outcomes: (a) PTB, (b) VPTB, (c) LBW, (d) VLBW, (e) SGA, (f) VSGA, and (g) neonatal death. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; LBW, low birthweight; Precon, preconception; PTB, preterm birth; RR, relative risk; SGA, small for gestational age; VLBW, very low birthweight; VPTB, very preterm birth; VSGA, very small for gestational age.

(e)



(f)



(g)



FIGURE 2 (Continued)

TABLE 3 Random-effects meta-analysis results for relative risk of perinatal outcomes for different comparisons of timing of ART initiation. (a) All studies. (b) Studies conducted in high-income countries. (c) Studies conducted in low- and middle-income countries

Perinatal outcome							
Timing of ART initiation	Preterm birth	Very preterm birth	Low birthweight	Very low birthweight	Small for gestational age	Very small for gestational age	Neonatal death
(a) All studies							
Preconception vs antenatal	1.16 (1.03–1.31)	1.16 (0.90–1.49)	1.08 (0.91–1.28)	1.12 (0.76–1.66)	1.04 (0.83–1.30)	0.89 (0.60–1.32)	0.93 (0.59–1.47)
Preconception/T1 vs T2/T3	1.08 (0.95–1.24)	1.18 (0.97–1.43)	1.06 (0.88–1.28)	0.98 (0.71–1.33)	0.96 (0.82–1.12)	0.71 (0.38–1.30)	1.24 (0.75–2.06)
T1 vs T2	1.09 (0.99–1.21)	1.04 (0.81–1.33)	1.17 (0.79–1.71)	1.03 (0.71–1.49)	1.09 (0.80–1.49)	0.86 (0.62–1.19)	1.53 (0.87–2.68)
T2 vs T3	0.97 (0.61–1.54)	5.64 (2.70–11.78)	0.88 (0.57–1.37)	8.66 (0.51–146.11)	0.81 (0.56–1.18)	3.97 (0.56–28.16)	
T1 vs T3	1.19 (0.91–1.55)	5.39 (2.41–12.09)	1.32 (0.80–2.17)	10.97 (0.60–202.14)	1.01 (0.64–1.59)	2.42 (0.27–21.63)	
(b) High-income countries							
Preconception vs antenatal	1.07 (0.87–1.31)	1.47 (1.19–1.82)	0.60 (0.17–2.16)	1.75 (0.98–3.11)	0.92 (0.63–1.36)	0.28 (0.07–1.16)	
Preconception/T1 vs T2/T3	1.21 (0.96–1.51)	1.41 (1.11–1.78)			0.71 (0.44–1.14)	0.43 (0.17–1.10)	
T1 vs T2	1.98 (0.33–12.02)	0.90 (0.58–1.41)			0.76 (0.38–1.51)	0.61 (0.19–1.92)	
T2 vs T3	1.08 (0.46–2.53)	5.44 (2.54–11.66)			1.07 (0.55–2.08)	3.97 (0.56–28.16)	
T1 vs T3	1.32 (1.05–1.66)	4.92 (2.12–11.40)			0.81 (0.34–1.94)	2.42 (0.27–21.63)	
(c) Low- and middle-income countries							
Preconception vs antenatal	1.15 (0.97–1.36)	0.95 (0.74–1.21)	1.07 (0.91–1.25)	0.89 (0.60–1.33)	1.08 (0.82–1.43)	1.00 (0.79–1.26)	0.93 (0.59–1.47)
Preconception/T1 vs T2/T3	1.01 (0.85–1.19)	1.04 (0.83–1.29)	1.06 (0.88–1.28)	0.98 (0.71–1.33)	0.99 (0.86–1.14)	0.86 (0.65–1.14)	1.24 (0.75–2.06)
T1 vs T2	1.11 (0.98–1.26)	1.10 (0.82–1.49)	1.17 (0.79–1.71)	1.03 (0.71–1.49)	1.19 (0.80–1.75)	0.88 (0.63–1.24)	1.53 (0.87–2.68)
T2 vs T3	0.78 (0.57–1.07)	9.33 (0.56–156.74)	0.88 (0.57–1.37)	8.66 (0.51–146.11)	0.71 (0.45–1.12)		
T1 vs T3	0.94 (0.64–1.39)	15.85 (0.90–279.01)	1.32 (0.80–2.17)	10.97 (0.60–202.14)	1.10 (0.65–1.87)		

Notes. Data are presented as RR (95% CI). Random-effects meta-analysis results for perinatal outcomes for different timings of ART initiation comparisons. A RR > 1 indicates that the first-mentioned timing of ART initiation is associated with an increased risk of the corresponding perinatal outcome relative to the second-mentioned timing of ART initiation.

Abbreviations: CI, confidence interval; RR, relative risk; T1, first trimester; T2, second trimester; T3, third trimester.

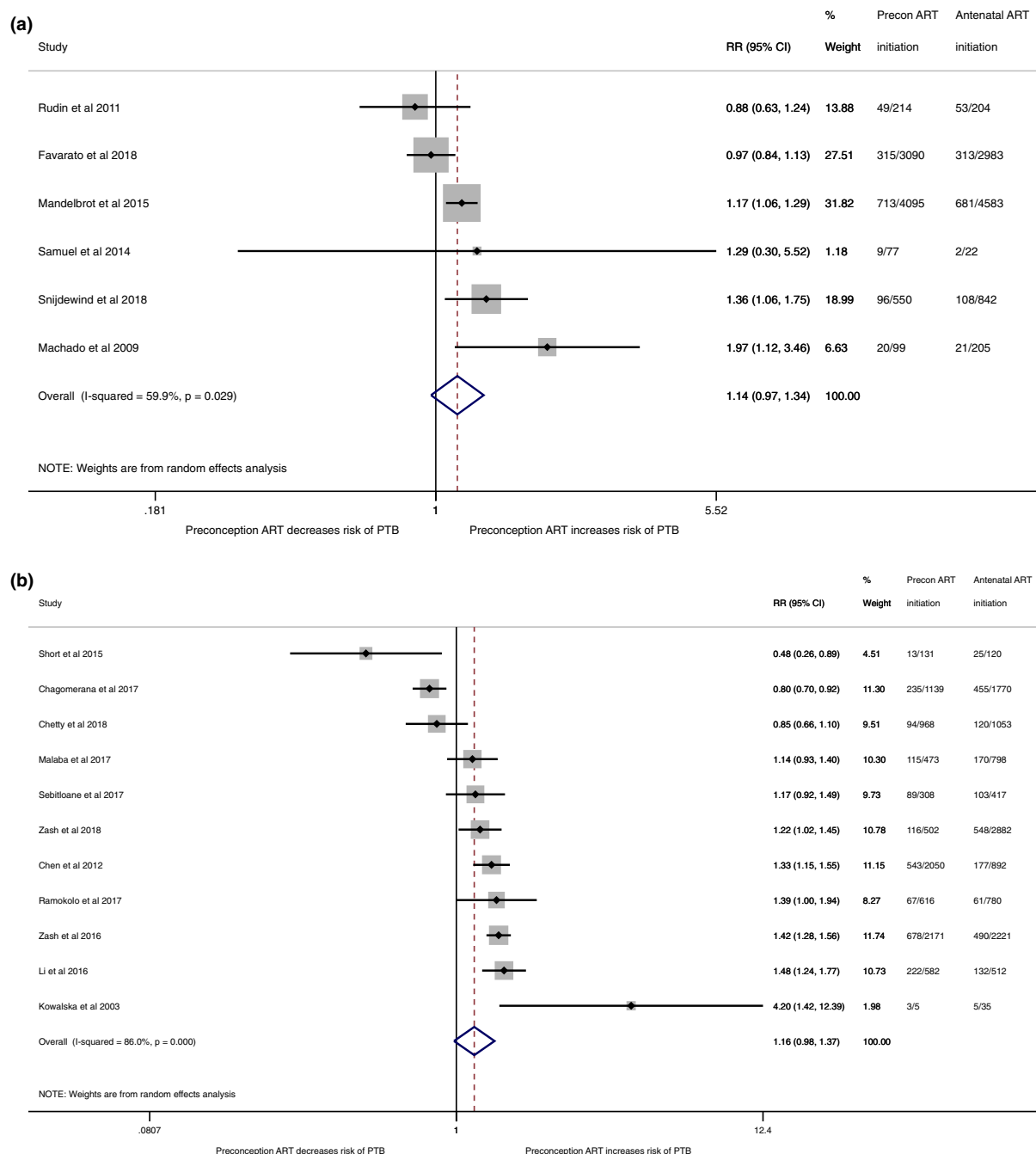


FIGURE 3 ART regimens and risk of PTB associated with preconception compared to antenatal ART initiation. Forest plots depicting RR and 95% CI of random-effects meta-analysis of risk of PTB associated with preconception versus antenatal ART association for studies in which the majority of women received (a) PI-based ART or (b) non-PI-based ART. Detailed information on ART regimens according to timing of ART initiation is presented in Appendix 3.1. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; PI, protease inhibitor; Precon, preconception; PTB, preterm birth; RR, relative risk.

studies involving PI-based ART and non-PI-based ART (Table 3, Appendix 5.2, Figure 3).

In total, 38 293 women from 24 studies were included in the comparison of preconception versus antenatal initiation of ART [6, 16, 18, 30–51]. Preconception ART initiation was significantly associated with preterm birth (RR 1.16; 95% CI 1.03–1.31) (Figure 2a, Table 3a). There was a high level of heterogeneity ($I^2 = 81.4\%$) (Appendix 4.1) but

no evidence of publication bias (Peters' test, $p = 0.526$). Sensitivity analysis was conducted in which the study with the largest effect size [36] was removed, which gave a very similar result (RR 1.14; 95% CI 1.02–1.29) (Appendix 5.1). There were no significant associations between preconception ART initiation and very preterm birth (RR 1.16; 95% CI 0.90–1.49), low birthweight (RR 1.08; 95% CI 0.91–1.28), very low birthweight (RR 1.12; 95% CI 0.76–1.66), small for

gestational age (RR 1.04; 95% CI 0.83–1.30), very small for gestational age (RR 0.89; 95% CI 0.60–1.32), and neonatal death (RR 0.93; 95% CI 0.59–1.47) (Figure 2b–g and Table 3a). No significant association between preconception ART initiation and any perinatal outcome was seen in LMICs and average-quality studies, but preconception ART initiation was significantly associated with preterm birth in poor-quality studies (RR 1.17; 95% CI 1.03–1.34; Table 3c; Appendix 5.2). A significant association between preconception ART initiation and very preterm birth was found in the two studies conducted in HICs (RR 1.47; 95% CI 1.19–1.82; Table 3b).

A total of 18 666 women from seven studies were included in the comparison of preconception/first trimester (preconception/T1) and second/third trimester (T2/T3) initiation of ART [6, 30, 32, 36, 39, 49, 50]. No significant association was found between first trimester ART exposure and any of the perinatal outcomes (Table 3a). A significant association between first trimester ART exposure and very preterm birth was seen in the single poor-quality study, which was conducted in an HIC (RR 1.41; 95% CI 1.11–1.78) (Table 3b; Appendix 5.2). No significant association between first trimester ART exposure and any perinatal outcomes was seen in studies of average quality and those conducted in LMICs (Table 3c; Appendix 5.2).

In total, 16 748 women from six studies were included in comparisons between trimesters of antenatal ART initiation; 8928 women from six studies were included in the comparison of T1 and T2 ART initiation [6, 30, 32, 36, 39, 50]. No significant association was found with any perinatal outcome, either in all studies analysed together or the HIC/LMIC and poor/average-quality subgroups (Table 3; Appendix 5.2).

In total, 4664 women from four studies were included in the comparison of T2 and T3 ART initiation [6, 30, 36, 39]. T2 ART initiation was significantly associated with very preterm birth (RR 5.64; 95% CI 2.70–11.78; Table 3a). The association was only significant in the poor-quality study from an HIC (RR 5.44; 95% CI 2.54–11.66) (Table 3b; Appendix 5.2). This association was not seen in the average-quality study conducted in an LMIC (RR 9.33; 95% CI 0.56–156.74; Table 3c; Appendix 5.2).

In total, 2166 women from four studies were included in the comparison of T1 and T3 ART initiation [6, 30, 36, 39]. T1 ART initiation was significantly associated with very preterm birth (RR 5.39; 95% CI 2.41–12.09) (Table 3a). This association was only significant in a poor-quality study from an HIC (RR 4.92; 95% CI 2.12–11.40). An increased risk of preterm birth when ART was initiated in T1 was reported in two poor-quality studies in HICs (RR 1.32; 95% CI 1.05–1.66; Table 3b; Appendix 5.2). No significant associations

with any outcomes were seen in studies of average quality and those conducted in LMICs (Table 3c; Appendix 5.2).

As there is evidence that PI-based ART may be associated with preterm birth, we conducted subgroup analyses for studies in which the majority of women received either PI-based ART or non-PI-based ART (Table 2; Appendix 3.1). The pooled risk of preterm birth with preconception ART, compared with antenatal ART, in studies with mostly PI-based ART (RR 1.14; 95% CI 0.97–1.34; Figure 3a) was nearly identical to that observed for studies with mostly non-PI-based ART (mainly non-nucleoside reverse transcriptase inhibitor [NNRTI]) (RR 1.16; 95% CI 0.98–1.37; Figure 3b), and neither were statistically significant.

Subgroup analysis of studies that excluded multiple pregnancies (i.e. twins) showed no statistically significant associations between timing of ART initiation and either preterm birth or very preterm birth (Appendix 8).

DISCUSSION

This systematic review and meta-analysis found that preconception ART initiation, compared with antenatal ART initiation, significantly increased the risk of preterm birth but not very preterm birth, low birthweight, very low birthweight, small for gestational age, very small for gestational age, and neonatal death. First trimester exposure (i.e. preconception/T1 ART initiation) was not significantly associated with any adverse outcomes. No significant associations between timing of ART initiation and adverse perinatal outcomes were found in studies conducted in LMICs, where most pregnant women living with HIV reside and an increasing number initiate ART before conception. Given the benefits of preconception ART initiation for maternal health and optimal prevention of vertical transmission of HIV, the WHO recommendation for immediate ART initiation in all people living with HIV, including pregnant women and those of childbearing potential, remains essential.

This study has several strengths. Our systematic review and meta-analysis is the largest to date, including 25 cohort studies and data from 40 920 pregnancies, to assess the effect of timing of ART initiation on specific adverse perinatal outcomes. Our study was conducted according to Cochrane guidelines, and at least two investigators conducted each step independently. Outcomes were clearly defined and strictly applied, which reduced misclassification bias. Eligible papers were cross-checked to prevent the inclusion of largely overlapping studies (Appendix 6.2). A random-effects meta-analysis model was used and several subgroup and sensitivity analyses

were conducted. Where applicable, the Peters' test confirmed an absence of publication bias. The majority of the studies and data analysed were from LMICs, which have the highest burden of both maternal HIV infection and adverse perinatal outcomes, thereby enhancing the external validity of our findings. The study was reported according to the PRISMA guidelines, thereby minimizing reporting bias.

Our findings contrast with the findings of a previous meta-analysis, which reported increased risks of preterm birth, very preterm birth, and low birthweight associated with preconception ART compared with antenatal ART initiation [53]. However, there are several notable differences between our studies. Our more recent study included 25 studies compared with 11 and include data from 40 920 pregnancies instead of 19 189. In the comparison of preconception versus antenatal ART initiation, our study included 17 additional papers and excluded four papers that Uthman et al. [53] included. Of the 17 new papers, 10 were published after the Uthman search end date (June 2016) [53], whereas seven were published within the Uthman search period but were omitted for reasons unknown (Appendix 6.1). In addition, we assessed the associations of trimesters of antenatal ART initiation with perinatal outcomes as well as gestational age estimation methods and individual study quality.

This study has some limitations. All included studies were observational (i.e. cohorts) as no relevant RCTs were identified. However, cohort studies may provide a more accurate representation of ART regimens and timings of ART initiation experienced by pregnant women in the real world. The perinatal outcomes very preterm birth, very low birthweight, very small for gestational age, and neonatal death were reported in a limited number of included studies, and several comparisons of timing of ART initiation were also reported by few studies. As a result, several of the (meta-)analyses included very few studies, which reduced the reliability of these findings. Notably, the significant associations found for very preterm birth rely on only two studies, including one poor-quality study from an HIC [6], leaving significant uncertainty regarding the true associations.

Ten studies did not give information on how gestational age was established, and only one study used first trimester ultrasound [37], which is the most accurate method of estimating gestational age [52]. Inaccurate assessment of gestational age and limited adjustment for confounding were the main reasons that 72% of studies were judged to be of poor quality, with similar proportions of poor-quality studies conducted in HICs (75%) and LMICs (69%). Poor study quality means a higher risk of bias and confounding, which may have produced inaccurate results and increased heterogeneity. Small for

gestational age and very small for gestational age cut-offs were based on centile charts used by each study rather than international standards [26]. Finally, because of the lack of universally accepted definitions of the gestational week boundaries of each trimester, we adopted a pragmatic approach to accept the definitions used by each study, even if undefined (Appendix 3.2).

Although different timings of ART initiation lead to different durations of ART exposure in pregnant women, they also lead to inevitable selection bias [54]. Pregnant women who start ART in pregnancy will have less opportunity to experience adverse birth outcomes than women who start ART preconception, and some adverse outcomes may occur before women commence ART during pregnancy. The same is true for comparisons between different trimesters of antenatal ART initiation. This effect is more pronounced for more severe outcomes and may explain why very preterm birth rates were higher when ART was initiated in trimesters 1 and 2 compared with 3, as the start of trimester 3 (~week 26–28) is very close to the cut-off for very preterm birth (<32 weeks). In addition, women who initiated ART late in pregnancy may differ from women who initiated ART earlier (e.g. poor access to care or new HIV diagnosis), which may confound the association with adverse pregnancy outcomes.

A further confounder in included studies is indication bias between the preconception and antenatal ART initiation groups, as preconception ART was initiated for maternal reasons (i.e. low CD4 count), whereas antenatal ART was initiated for either prevention of vertical HIV transmission (at high CD4 counts) or for maternal reasons (low CD4 count). Eight (32%) studies corrected for CD4 count (Appendix 2.5–2.6).

Inclusion of twins may have affected some results, as a subgroup analysis of studies that excluded twins showed no significant association between timing of ART initiation and either preterm birth or very preterm birth (Appendix 8). However, this subgroup analysis contained fewer studies, particularly for the comparison between preconception and antenatal ART initiation. None of the studies that included twins corrected for twins in their analysis (Appendix 2.5–2.6). These findings mean the possibility remains that timing of ART initiation is not associated with preterm birth or very preterm birth in singleton pregnancies.

For most studies, the ART regimens differed between ART initiation arms or only details of the regimen(s) used in the study as a whole were given. There is ample, but conflicting, evidence regarding the association of ART regimens with risk of adverse perinatal outcomes, and the differences in ART regimen received by different ART initiation groups may therefore have influenced the outcomes [14, 15]. Of the nine studies that conducted

regression analysis, only two adjusted for ART regimen (Appendix 2.5–2.6) [30, 34].

During our study period, PI-based ART was generally recommended for use in pregnancy in HICs, whereas NNRTI-based ART was recommended in LMICs. As there is evidence that PI-ART may be associated with preterm birth [20, 21, 23, 55], we examined the association between preconception ART and preterm birth in studies with PI-based ART and those with non-PI-based ART. We found that the pooled risk of preterm birth with preconception ART, compared with antenatal ART, in studies with mostly PI-based ART was nearly identical to that observed for studies with mostly non-PI-based ART, and both were non-significant. Therefore, in studies included in our analysis, there was no interaction between class of ART (PI-based or non-PI-based) and the association between preconception ART and preterm birth. The type of ART regimen is therefore unlikely to account for the different associations seen in HICs and LMICs in our study. A factor that may have contributed to the higher risks of preterm birth and very preterm birth associated with earlier ART initiation observed in HICs, but not LMICs, might be the overall lower levels of adverse perinatal outcomes in populations in HICs, which would enable detection of a small absolute increase in risk.

Current WHO guidance recommends dolutegravir-containing regimens as preferred first- and second-line ART, including for women of childbearing potential and pregnant women [56]. Unfortunately, no studies included in our analysis contained participants receiving dolutegravir-containing regimens. A recent retrospective study from Botswana showed that the prevalence of neural tube defects was slightly higher with dolutegravir exposure at conception than with other regimens (0.2% excess risk) [57]. Congenital abnormalities were not one of our selected outcomes, as few published data are available [53]. Only one of the studies included in our analysis reported congenital abnormalities, and this outcome was not significantly different between the preconception and antenatal initiation groups (RR 1.01; 95% CI 0.04–24.14) [45].

The same study from Botswana reported that other adverse perinatal outcomes were comparable between women living with HIV receiving dolutegravir-based and efavirenz-based ART [57, 58]. Recent RCTs of ART regimens initiated during pregnancy showed that the virological efficacy of dolutegravir-containing regimens was superior to that of efavirenz-based ART [59, 60] and that a regimen containing dolutegravir, emtricitabine, and tenofovir alafenamide fumarate had the lowest rate of adverse pregnancy outcomes [60]. However, it is clear that adverse perinatal outcomes remain significantly higher among women living with HIV on either

dolutegravir-based, efavirenz-based, or other regimens compared with women without HIV [14, 55, 57, 58, 61].

The biological mechanisms contributing to the associations between HIV, ART, and adverse perinatal outcomes remain unclear. The pathogenesis underlying adverse perinatal outcomes is multifaceted, and the cause is often unknown, regardless of HIV infection status [62]. HIV infection is associated with CD4 depletion and chronic immune activation, which may affect the immunological programme of pregnancy [63]. Several innate immune cells, including innate lymphoid cells and mucosal-associated invariant T cells, are depleted during early HIV infection and fail to recover with ART and may be associated with an increased risk of adverse perinatal outcomes [64, 65]. One hypothesis proposes an immune-mediated mechanism in which ART causes a type 2 T-helper cell (Th₂) to Th₁ shift that counteracts the Th₁ to Th₂ shift seen in pregnancy and ART-naïve HIV infection [66]. The effect of ART initiation on the immune response may be more pronounced in early pregnancy and may explain why earlier ART initiation was associated with higher rates of preterm birth and very preterm birth. Another hypothesis suggests inhibition of placental progesterone production by PIs as a potential mechanism contributing to foetal growth restriction [67].

Given the benefits of ART for maternal health and prevention of vertical transmission of HIV, immediate ART initiation in all people living with HIV, including pregnant women and those of childbearing potential, is crucial. However, it is of paramount importance to determine the optimal ART regimen for use in pregnancy and to better understand the mechanisms that lead to adverse outcomes in the context of maternal HIV/ART to devise predictive, preventive, and therapeutic interventions to reduce the incidence and impact of these adverse perinatal outcomes.

AUTHOR CONTRIBUTIONS

HS, MK, ZB, and CS screened the literature search results for relevant manuscripts and assessed their eligibility, extracted data, and conducted methodological quality assessments. HS conducted the meta-analyses and subgroup and sensitivity analyses, interpreted the data, and wrote the first draft of the manuscript. SK designed and conducted the literature search. JH conceived, designed, and coordinated the study; developed the systematic review protocol; assisted with the literature search, assessment of eligibility of manuscripts, data extraction, and methodological quality assessment; designed the meta-analysis plan; interpreted the data; and wrote the manuscript. JH had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Study data are available on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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