Adverse perinatal outcomes associated with HAART and monotherapy

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Objectives: Assess adverse perinatal outcomes in pregnant women living with HIV (WLHIV) receiving HAART or zidovudine (ZDV) monotherapy, compared with antiretroviral therapy (ART)-naive WLHIV and HIV-negative women.

Design: Systematic review and meta-analysis.

Methods: We conducted a systematic literature review by searching PubMed, CINAHL, Global Health, and EMBASE for studies published between 1 January 1980 and 20 April 2020. We included studies reporting on the association of pregnant WLHIV receiving HAART or ZDV monotherapy with 11 perinatal outcomes: preterm birth (PTB), very PTB, spontaneous PTB (sPTB), low birth weight (LBW), very LBW, term LBW, preterm LBW, small for gestational age (SGA), very SGA (VSGA), stillbirth, and neonatal death. Random-effects meta-analyses were conducted.

Results: Sixty-one cohort studies assessing 409 781 pregnant women were included. WLHIV receiving ZDV monotherapy were associated with a decreased risk of PTB [relative risk 0.70, 95% confidence interval (CI) 0.62–0.79] and LBW (0.77, 0.67–0.88), and comparable risk of SGA, compared with ART-naive WLHIV. WLHIV receiving ZDV monotherapy had a comparable risk of PTB and LBW, and an increased risk of SGA (1.16, 1.04–1.30) compared with HIV-negative women. In contrast, WLHIV receiving HAART were associated with a comparable risk of PTB and LBW, and increased risk of SGA (1.38, 1.09–1.75), compared with ART-naive WLHIV. WLHIV receiving HAART were associated with an increased risk of PTB (1.55, 1.38–1.74), sPTB (2.09, 1.48–2.96), LBW (1.79, 1.51–2.13), term LBW (1.88, 1.23–2.85), SGA (1.80,1.34–2.40), and VSGA (1.22, 1.10–1.34) compared with HIV-negative women.

Conclusion: Pregnant WLHIV receiving HAART have an increased risk of a wide range of perinatal outcomes compared with HIV-negative women.

AIDS 2022, **36**:1409–1427

Keywords: antiretroviral therapy, HIV, low birthweight, meta-analysis, neonatal death, perinatal outcome, preterm birth, small for gestational age, stillbirth, systematic review

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Received: 17 November 2021; revised: 4 April 2022; accepted: 4 April 2022.

DOI:10.1097/QAD.0000000000003248

Introduction

In 2020, 37.7 million people worldwide were living with HIV, including 19.3 million women of childbearing age [1]. Each year, an estimated 1.3 million women living with HIV (WLHIV) are pregnant, of whom the vast majority reside in sub-Saharan Africa [1]. Antiretroviral therapy (ART)-naive maternal HIV infection is associated with an increased risk of preterm birth (PTB), low birthweight (LBW), small for gestational age (SGA), and stillbirth compared with HIV-negative women [2]. Adverse perinatal outcomes are major contributors to neonatal and child mortality and morbidity, with the highest rates found in sub-Saharan Africa [3–5]. The United Nations' Sustainable Development Goal 3 (SDG3) target 3.2 aims to reduce neonatal and under-5 mortality to 12 and 25 per 1000 live births, respectively, by 2030 [6].

In 1994, a randomized controlled trial (RCT) demonstrated that antenatal zidovudine (ZDV) monotherapy reduced the risk of mother-to-child HIV transmission [7]. In the past, WHO guidelines recommended ZDV monotherapy in pregnant WLHIV to prevent vertical HIV transmission (option A), or HAART for pregnant WLHIV requiring treatment for their own health as well as prevention of vertical HIV transmission (option B) [8]. From 2013, WHO recommended that all pregnant WLHIV should receive HAART during pregnancy [9]. In 2015, this recommendation was updated so that all people living with HIV should initiate HAART as soon as possible after diagnosis, including pregnant WLHIV [10]. Consequently, the proportion of pregnant WLHIV receiving ZDV monotherapy decreased from 31 to 0% in the period 2011–2020, whereas the proportion of pregnant WLHIV receiving HAART increased from 27 to 83% during the same period [1]. These trends were accompanied by a 41% reduction in vertical HIV transmission globally during 2010–2018 [11]. However, the impact of these changes in antenatal ART regimens on other important perinatal outcomes is unknown.

Several studies suggest adverse perinatal outcomes are associated with ART exposure during pregnancy but evidence is conflicting regarding different regimens [12–15]. A recent network meta-analysis of seven randomized controlled trials (RCTs), which compared ART regimens initiated during pregnancy, showed that a number of HAART regimens were associated with an increased risk of LBW, very LBW and PTB, compared with ZDV monotherapy [16]. Some cohort studies report that HAART exposure is associated with increased risk of PTB and LBW in pregnant WLHIV, whereas ZDV monotherapy is not [17,18]. However, others report no significant association [19].

As the number of pregnancies exposed to HAART increases and ZDV monotherapy has been phased out, it is important to understand the effects of HAART and ZDV monotherapy on perinatal outcomes in WLHIV, and whether either therapy restores the risk of perinatal outcomes to levels seen in HIV-negative women. We conducted a systematic review and meta-analysis of cohort studies examining the risk of 11 specific perinatal outcomes in WLHIV receiving HAART or ZDV monotherapy, compared with ART-naive WLHIV and HIV-negative women.

Methods

Search strategy

The systematic review and meta-analyses were conducted according to a protocol developed in line with the Cochrane guidelines [20] and registered online (PROSPERO, number CRD42021248987). A comprehensive literature search strategy, developed by a specialist librarian (S.K.), was adapted to four electronic literature databases [PubMed, CINAHL (Ebscohost), Global Health (Ovid), EMBASE (Ovid)] to search for studies published 1 January 1980–20 April 2020. Both free text and controlled vocabulary search terms for 'pregnancy outcome', 'specific perinatal outcomes', 'HIV', and 'antiretroviral therapy' were used (Appendix pp. 2–14, http://links.lww.com/QAD/C513). Full-text articles and abstracts were considered, and no methodological, country, or language filters were applied. Retrieved citations were imported into EndNote (EndNote X9, Clarivate Analytics, Pennsylvania, USA) and deduplicated.

Study selection and eligibility criteria

Studies that contained information on the association of pregnant WLHIV receiving HAART or monotherapy (in distinct groups) with adverse perinatal outcomes were eligible. Titles and abstracts of citations were reviewed, and full text manuscripts of selected citations assessed against the eligibility criteria by at least two independent investigators (C.P., H.S., M.K., Z.B., and B.J.). Inclusion criteria were study design (cohort studies), population (pregnant women), exposure (WLHIV receiving HAART or monotherapy during pregnancy), comparators (ART-naive WLHIV or HIV-negative women). Monotherapy exposure was defined as receiving one antiretroviral drug (ZDV) during pregnancy. HAART exposure was defined as receiving any class and combination of at least three antiretroviral drugs. Single dose ART at birth or antenatal ART duration less than 30 days were not considered ART exposure. Studies were excluded if one group received a treatment, which the comparator group did not (e.g. antimalaria treatment), or if less than 95% of women in a group conformed to an exposure/comparator definition (e.g. <95% WLHIV received HAART). Studies were excluded if outcome data were not stratified by either monotherapy or HAART exposure. Perinatal outcomes of interest were

defined as follows: PTB ($<37^{+0}$ weeks gestation) [21]; very PTB (VPTB, $<32^{+0}$ weeks gestation) [21]; spontaneous PTB (sPTB, spontaneous birth $<37^{+0}$ weeks gestation) [21]; LBW (<2500 g) [4]; very LBW (VLBW, <1500 g) [4]; SGA (birthweight for gestational age less than the tenth centile) [22]; very SGA (VSGA, birthweight for gestational age less than the third centile) [22], stillbirth (delivery of infant without signs of life with birthweight at least 1000 g or gestational age at least 24^{+0} weeks or body length at least 35 cm [23]; and neonatal death (NND, death of infant in first 28 days of life) [23]. Term and preterm LBW were defined according to definitions of PTB and LBW. Perinatal outcome data were not included if outcomes were not defined or if defined differently from our definitions. The study that contained the most recent and complete data was included if a cohort was reported on more than once. If multiple studies reported different perinatal outcomes for the same cohort, each study was included. References of studies meeting the inclusion criteria were assessed for additional studies. Ambiguities regarding inclusion of studies were resolved through discussion with the senior investigator (J.H.).

Data extraction

Data on study characteristics, HIV/ART exposures and perinatal outcomes were extracted from eligible studies by at least two investigators (C.P., H.S., M.K., Z.B., and B.J.) and reviewed by the senior investigator (J.H.). Perinatal outcome data according to exposure categories were extracted. Methods to adjust for confounders, including regression analysis, risk factor analysis, and matching, were extracted. Reported unadjusted and adjusted relative risks (RR), odds ratios (OR), and 95% confidence intervals (CIs) of perinatal outcomes according to HIV/ART exposure were also extracted.

Quality assessment

An adapted Newcastle–Ottawa Scale [24] was used to assess the quality of each individual study by at least two investigators (C.P., H.S., M.K., Z.B., and B.J.) and reviewed by the senior investigator (J.H.). Nine criteria were assessed in three groups: selection of study participants, comparability of comparator groups, and assessment of outcomes of interest. Studies were defined as 'good', 'average', or 'poor' quality according to predefined criteria (Appendix, pp. 15–17, http://links.lww.com/QAD/C513).

Statistical analysis

Perinatal outcomes were compared between WLHIV receiving either HAART or monotherapy, and ART-naive WLHIV or HIV-negative women. RRs and 95% CIs were generated from dichotomous outcome data according to HIV/ART exposure in individual studies. If two or more studies reported data for the same perinatal outcome for specified exposure and comparator groups, a pairwise meta-analysis was carried out. For all meta-analyses, a random-effects model was used to calculate a weighted summary effect estimate (RR) and 95% CI. Meta-analyses were represented in forest plots and the I^2 statistic was used to quantify heterogeneity because of clinical and methodological variability between studies. The degree of heterogeneity was classified as none (<25%), low (25–49%), moderate (50–74%), or high (≥75%). Subgroup analyses assessed the effects of country income status and sensitivity analyses investigated whether study quality and the adjustment for confounders impacted the associations between HIV/ART exposure and perinatal outcomes. Peters' test was used to assess publication bias in meta-analyses containing at least 10 studies. All statistical analyses were done with Stata version 15 (College Station, Texas, USA). The systematic review is reported according to the PRISMA guidelines [25].

Role of funding sources

This study received no funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The literature search yielded 94 594 citations, of which 61 studies reported relevant data (Fig. 1). The numbers of studies reporting different perinatal outcomes for the comparisons of WLHIV receiving HAART or ZDV monotherapy with ART-naive WLHIV and HIV-negative women are displayed in Fig. 1.

Characteristics of included studies are summarised in Table 1 [13,18,19,26–82]. Twenty-six (43%) prospective and 35 (57%) retrospective cohort studies analysed data from 409 781 women in 27 countries (Table 1). Thirty-one (51%) studies with 59 890 (15%) women took place in high-income countries (HICs), and 30 (49%) studies with 349 891 (85%) women took place in low-income and middle-income countries (LMICs) (Table 1). Forty-two (69%) studies reported the methods used to determine gestational age, with four (7%) studies using first trimester ultrasound (Table 1). Forty-eight (79%) studies used methods to assess potential confounding factors, including regression analysis, risk factor analysis, and matching (Table 1, Appendix, pp. 25–29, http://links.lww.com/QAD/C513). Of the 22 analyses, which were adjusted for covariates by regression analysis in individual studies, only two resulted in a change in the significance of the effect estimate (Appendix, pp. 59–62, http://links.lww.com/QAD/C513). Quality assessments classified 30 (49%) studies as poor quality, 30 (49%) as average quality and one (2%) as good quality (Table 1, Appendix, pp. 18–24, http://links.lww.com/QAD/C513).

The ART regimens received by WLHIV, exposure comparisons reported, and perinatal outcomes analysed are displayed for each study in Table 2.

Fig. 1. Study selection. *For example, women living with HIV were not pregnant. †For example, article did not provide relevant outcome data. ‡For example, Assisted Reproductive Technology (ART). ART, antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birthweight; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous preterm birth; VLBW, very low birthweight; VPTB, very preterm birth; VSGA, very small for gestational age; WLHIV, women living with HIV. See Methods for definitions of perinatal outcomes.

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

Study: first author (year) [ref]	Country	Country income status	Cohort study design	Recruitment period	Number of women analysed	Population characteristics[a]	Method to correct for confounders	Method to estimate gestational age	Quality assessment
Ai-Jie (2013) [26]	China	Middle	Retrospective	1/2006 to 3/2008	155	Twins excluded, rural and urban setting	None	No description	Poor
Albert (2020) [27]	Canada	High	Retrospective	1/1/1997 to 31/1/2018	477	Twins excluded, women recruited from a provincial surveillance database, 46.1% smoking, 23.3% alcohol use, 26% IDU	Risk factor analysis	Ultrasound in first and/or second trimester	Average
Azria (2009) [28]	France	High	Retrospective	1/2003 to 6/2007	300	Twins excluded, women recruited from a level III maternity unit, urban setting, hospital deliveries, 4.3% smoking during pregnancy, 1.7% history of IDU	Risk factor analysis, matching	First day of LNMP, corrected if needed by routine first trimester ultrasound	Average
Bailey (2013) [29]	Ukraine	Middle	Retrospective	2008 to 2010	3535	First born twin included, hospital deliveries, 14.7% history of IDU	None	LNMP and ultrasound (unspecified)	Poor
Balogun (2018) [30]	Canada	High	Prospective	9/2010 to 12/2015	104	Twins excluded, women recruited from four sites in Toronto, 0% smoking	Risk factor analysis, matching	LNMP confirmed by ultrasound (unspecified)	Average
Bengtson (2020) [31]	South Africa	Middle	Prospective	3/2013 to 8/2015	1116	Twins excluded, women recruited from antenatal care clinics in Gugulethu Cape Town, urban setting, 17.2% alcohol use	None	Ultrasound (unspecified), LNMP, or symphysis-fundal height	Poor
Boer (2006) [32]	Netherlands	High	Retrospective	12/1997 to 7/2003	294	First born twin included, women recruited from an academic medical centre, 12.9% smoking, 1.7% history of IDU	Regression analysis, matching	LMNP confirmed by first trimester ultrasound	Poor
Boyajian (2012) [33]	Canada	High	Retrospective	1/1/2003 to 10/1/2010	364	Second twin excluded, women recruited from tertiary pregnancy referral centre, hospital deliveries, 6.3% smokers, 1.4% IDU	Regression analysis, risk factor analysis, matching	No description	Average
Carceller (2009) [34]	Canada	High	Retrospective	1997 to 2005	412	Recruited from a tertiary hospital in Montreal, urban setting, hospital deliveries	None	No description	Poor
Chagomerana (2017) [35]	Malawi	Low	Retrospective	1/4/2012 to 15/11/2015	3074	Twins excluded, urban setting, hospital deliveries	Regression analysis	LNMP	Average
Chen (2012) [36]	Botswana	Middle	Retrospective	1/5/2009 to 30/4/2011	33148	First born twin included, hospital deliveries, 5.3% alcohol use, 1.7% smoking	Regression analysis, risk factor analysis	LNMP, symphysis-fundal height, or ultrasound (unspecified)	Average
Chibwesha (2016) [37]	Zambia	Low	Retrospective	1/2/2006 to 31/12/2012	200557	First born twin included, women recruited from MNCH health system, urban setting	None	LNMP and symphysis-fundal height	Poor

Table 1 (*continued*)

Study: first author (year) [ref]	Country	Country income status	Cohort study design	Recruitment period	Number of women analysed	Population characteristics[a]	Method to correct for confounders	Method to estimate gestational age	Quality assessment
Cooper (2002) [38]	USA	High	Prospective	1/1990 to 6/2000	1542	Twins excluded, 31% IDU	Risk factor analysis	LNMP, ultrasound (unspecified), symphysis-fundal height, or neonatal assessment (unspecified)	Poor
Cotter (2006) [39]	USA	High	Prospective	1/1990 to 12/2002	1337	Twins excluded, 5.4% alcohol use, 11.2% smoking, 17.8% IDU, women recruited from medical centre, hospital deliveries	Regression analysis, risk factor analysis	LNMP and/or ultrasound (unspecified)	Poor
Dadabhai (2019) [40]	Malawi	Low	Prospective	1/2016 to 9/2017	1299	Twins excluded, 96% of deliveries occurred in healthcare facilities, urban setting	Regression analysis	Ballard score and LNMP	Average
De Souza (2000) [41]	USA	High	Retrospective	1/1/1990 to 31/12/1994	403	First born twin included, women recruited from a tertiary hospital, 18.9% IDU	Risk factor analysis	No description	Average
Garcia-Otero (2019) [42]	Spain	High	Prospective	12/2014 to 3/2017	94	Women recruited from hospital and hospital clinic, urban setting, 20.2% smoking, 3.2% IDU	Risk factor analysis	No description	Average
Goetghebuer (2019) [43]	Belgium	High	Prospective	12/2010 to 11/2013	255	Women recruited from hospital antenatal clinic, urban setting, 9.2% smoking, 10.1% alcohol use	Risk factor analysis	Ballard score	Average
Haeri (2009) [44]	USA	High	Retrospective	1/2000 to 1/2007	453	Women recruited from two tertiary care centres, 13.3% smoking	Regression analysis, risk factor analysis, matching	LNMP and ultrasound (unspecified)	Average
Hernandez (2017) [45]	Spain	High	Prospective	6/2006 to 12/2007	56	Twins excluded, women recruited from maternofetal medicine department of hospital, urban setting, 25% smoking, 0% alcohol use, 0% IDU	Risk factor analysis, matching	No description	Average
Hu (2019) [46]	China	Middle	Prospective	10/2009 to 5/2018	802	Twins included, urban setting	Regression analysis, risk factor analysis	First or second trimester ultrasound, in the absence of ultrasound LNMP used	Average
Joseph (2011) [47]	Nigeria	Middle	Retrospective	1/2008 to 6/2009	249	Twins excluded, women recruited from a tertiary referral centre, hospital deliveries	Risk factor analysis	No description	Average
Jumare (2019) [48]	Nigeria	Middle	Prospective	2013 to 2017	424	Twins included, women recruited from a specialist hospital, urban setting	Risk factor analysis	LNMP	Average
Kakkar (2015) [49]	Canada	High	Prospective	1988 to 2011	589	Twins excluded, women recruited from a tertiary referral centre and the largest maternal-health centre in the province	Regression analysis, risk factor analysis	LNMP and ultrasound (unspecified)	Average

Table 1 (*continued*)

Study: first author (year) [ref]	Country	Country income status	Cohort study design	Recruitment period	Number of women analysed	Population characteristics[a]	Method to correct for confounders	Method to estimate gestational age	Quality assessment
Kowalska (2003) [50]	Poland	Middle	Prospective	1/1995 to 2/2003	102	Twins included, women recruited from an outpatient HIV clinic, 47.1% IDU	Risk factor analysis	LNMP	Poor
Li (2016) [13]	Tanzania	Low	Prospective	11/2004 to 9/2011	3314	Women recruited from hospitals, health centres and dispensaries, urban setting	Risk factor analysis	LNMP and symphysis-fundal height	Poor
Li (2020) [51]	China	Middle	Prospective	10/2014 to 9/2017	1449	Twins excluded, women recruited from midwifery hospitals	Regression analysis, risk factor analysis	LNMP or ultrasound (unspecified)	Average
Liff (2020) [52]	Botswana	Middle	Prospective	4/2016 to 4/2017	179	Twins excluded, women recruited from 8 nationwide delivery sites	Risk factor analysis	Second trimester ultrasound	Poor
Lopez (2012) [53]	Spain	High	Retrospective	1/1986 to 6/2010	1557	Twins excluded, women recruited from a tertiary hospital, urban setting, hospital deliveries, 55.2% smoking	Regression analysis, risk factor analysis, matching	Second trimester ultrasound	Poor
Malaba (2017) [54]	South Africa	Middle	Prospective	4/2013 to 8/2015	1793	Twins excluded, recruited from large community primary care facility, urban setting	Regression analysis, risk factor analysis	LNMP and symphysis-fundal height	Average
Malaba (2018) [55]	South Africa	Middle	Prospective	4/2014 to 10/2016	1787	Twins excluded, women recruited from a large primary care antenatal clinic, urban setting	Regression analysis	LNMP and symphysis-fundal height	Average
Mandelbrot (1998) [56]	France	High	Retrospective	1/9/1985 to 31/12/1996	2834	Twins excluded, 31% IDU, recruited from obstetrical services, hospital deliveries	None	LNMP, confirmed by first trimester ultrasound	Poor
Marazzi (2011) [57]	Malawi and Mozambique	Low	Retrospective	7/2005 to 6/2009	3273	Twins included, women recruited from DREAM centres	Regression analysis	LNMP and clinical exam (unspecified)	Average
Marti (2007) [58]	Spain	High	Prospective	1/1/1997 to 31/12/2003	167	Twins excluded, women recruited from hospital, hospital deliveries, urban setting, 1% IDU	None	No description	Poor
Matheson (1995) [59]	USA	High	Prospective	3/1986 to 12/1993	321	Twins excluded, 41.7% IDU	Risk factor analysis	Ballard score	Average
Mehta (2019) [60]	South Africa	Middle	Retrospective	7/10/2013 to 6/10/2014	10293	Twins included, women recruited from hospital, urban setting, hospital deliveries, 0.09% smoking, 0.2% alcohol use, 0.04% IDU	Risk factor analysis	LNMP, ultrasound (unspecified)	Average
Moodley (2016) [61]	South Africa	Middle	Retrospective	7/2011 to 12/2011, 1/2014 to 6/2014	9847	Twins excluded, data abstracted from maternity registers of a regional hospital	Regression analysis, risk factor analysis	LNMP and/or ultrasound (unspecified)	Average

Table 1 (*continued*)

Study: first author (year) [ref]	Country	Country income status	Cohort study design	Recruitment period	Number of women analysed	Population characteristics[a]	Method to correct for confounders	Method to estimate gestational age	Quality assessment
Moseholm (2019) [62]	Denmark	High	Retrospective	1/1/2000 to 31/12/2016	2980	Twins excluded, women recruited from specialized clinical centres for treatment and care of pregnant women living with HIV, 7.6% smoking during pregnancy	Risk factor analysis, matching	No description	Average
Olagbuji (2010) [63]	Nigeria	Middle	Prospective	1/2007 to 12/2008	406	Twins excluded, women recruited from a tertiary referral centre, all delivered in a healthcare facility	Risk factor analysis	No description	Poor
Phiri (2015) [64]	USA	High	Retrospective	1/1/1994 to 31/12/2009	790	6.7% alcohol use, 25% smoking, 11% IDU	Regression analysis	LNMP, ultrasound (unspecified), and clinical assessment	Poor
Ramokolo (2017) [65]	South Africa	Middle	Retrospective	10/2012 to 5/2013	8778	Women recruited from primary health facilities	Risk factor analysis	LNMP	Average
Rempis (2017) [66]	Uganda	Low	Retrospective	2/2013 to 12/2013	412	Twins excluded, all deliveries in a private referral hospital	Risk factor analysis	No description	Poor
Rudin (2011) [67]	Switzerland	High	Prospective	1984 to 2007	1040	Twins excluded, 22% smoking, 26% IDU	None	No description	Poor
Santosa (2019) [68]	South Africa	Middle	Prospective	28/5/2013 to 20/7/2016	633	Twins excluded, women recruited from hospital, 98.7% hospital deliveries, urban setting, 6.4% smoking, 8.2% alcohol	Regression analysis, risk factor analysis	Ultrasound <14 weeks	Good
Saums (2019) [69]	USA	High	Retrospective	2011 to 2018	3729	Women recruited from hospital, urban setting, hospital deliveries, 11.5% smoking, 2.9% alcohol use, 13.4% IDU	Risk factor analysis	No description	Average
Schulte (2007) [70]	USA	High	Retrospective	1989 to 2004	11231	27.6% history of IDU	Regression analysis	LNMP, ultrasound (unspecified), neonatal assessment (unspecified)	Poor
Sebitloane (2017) [71]	South Africa	Middle	Retrospective	1/4/2011 to 30/4/2014	1461	Twins excluded, women recruited at a regional hospital, urban setting, hospital deliveries	None	No description	Poor
Short (2014) [72]	United Kingdom	High	Retrospective	1996 to 2010	331	Twins included, women recruited from a HIV antenatal clinic, urban setting, deliveries in a tertiary hospital, 13% smoking	None	No description	Poor
Silverman (2010) [73]	Zambia	Low	Retrospective	Unspecified	1238	Twins included	Risk factor analysis	No description	Poor
Simonds (1998) [74]	USA	High	Retrospective	1985 to 12/1995	1366	Twins excluded, 18.4% IDU	None	Ballard score	Poor
Snijdewind (2018) [75]	Netherlands	High	Retrospective	1/1997 to 2/2015	10795	Twins excluded, women recruited from 26 nationwide sites, 10.8% smoking, 11.7% alcohol use, 0.6% IDU	Risk factor analysis	Early ultrasound or LNMP	Average
Tiam (2019) [76]	Lesotho	Middle	Prospective	6/2014 to 2/2016	1594	Women recruited from 14 mixed setting study centres across 3 districts, 91.6% delivered in a health facility	None	LNMP	Poor

Table 1 (*continued*)

Study: first author (year) [ref]	Country	Country income status	Cohort study design	Recruitment period	Number of women analysed	Population characteristics[a]	Method to correct for confounders	Method to estimate gestational age	Quality assessment
Townsend ECS (2010) [18]	Belgium, Denmark, Germany, Italy, Netherlands, Poland, Spain, Sweden, United Kingdom	High	Prospective	1990 to 2006	4253	Twins excluded, 35.4% IDU	Regression analysis	LNMP and/or ultrasound (unspecified)	Poor
Townsend NSHPC (2010) [18]	United Kingdom, Ireland	High	Prospective	1990 to 2006	6426	Women recruited from 205 hospitals across UK and Ireland, 4.4% IDU	Regression analysis	No description	Poor
Tuomala (2002) [19]	USA	High	Retrospective	1/1/1990 to 1998	3266	Twins excluded, women recruited from PACTS and WITS studies, and three single site studies, 39.9% tobacco use during pregnancy, 26.9% alcohol use during pregnancy, 28.7% IDU use during pregnancy	Regression analysis, risk factor analysis	LNMP and/or ultrasound (unspecified), or neonatal assessment (unspecified)	Average
Van der Merwe (2011) [77]	South Africa	Middle	Retrospective	10/2004 to 3/2007	1630	Twins excluded, women recruited from HIV referral centres including a tertiary hospital, 3.7% smoking, 3.9% alcohol use	Regression analysis, risk factor analysis	LNMP, ultrasound (unspecified), symphysis-fundal height, neonatal assessment (unspecified)	Poor
Von Linstow (2010) [78]	Denmark	High	Retrospective	1/6/1994 to 30/6/2008	255	Twins included, women recruited from six centres nationwide, all hospital deliveries, 15.4% smoking, 2.2% IDU	None	Late ultrasound at 18–20 weeks	Poor
Watts (2013) [79]	USA and Puerto Rico	High	Retrospective	2007 to 31/10/2010	1869	Twins excluded, 17% smoking, 8% alcohol use, 8% IDU	Regression analysis	Clinical method (unspecified) and ultrasound (unspecified)	Average
Yu (2012) [80]	China	Middle	Retrospective	6/2006 to 7/2010	194	Twins excluded, 8.8% IDU	Risk factor analysis	No description	Poor
Zash (2018) [81]	Botswana	Middle	Retrospective	15/8/2014 to 15/8/2016	57005	Twins excluded, women recruited from eight government hospitals, hospital deliveries, 8.3% alcohol or smoking in pregnancy	Regression analysis	LNMP and/or ultrasound (unspecified), or symphysis-fundal height	Average
Ziske (2013) [82]	Tanzania	Low	Prospective	9/2008 to 9/2009	144	Twins excluded, women recruited from antenatal care (HIV+ receiving ART) or maternity ward (HIV+ no ART), rural setting, hospital deliveries	Risk factor analysis	No description	Poor

[a]Details on the inclusion of twins, recruitment centre, urban/rural setting, deliveries at home/hospital, smoking, alcohol use, and IDU were sought and reported here if provided by each study. ART, antiretroviral therapy; IDU, illicit drug use; LNMP, last normal menstrual period.

Random-effects meta-analyses were conducted to compare perinatal outcomes in WLHIV receiving HAART or ZDV monotherapy with ART-naive WLHIV and HIV-negative women (Table 3a, Appendix, pp. 30–45, http://links.lww.com/QAD/C513). Subgroup analyses were carried out according to country income status (Table 3b) and study quality (Appendix, pp. 46–48, http://links.lww.com/QAD/C513).

In the analysis of 19 studies including 24 222 women, WLHIV receiving monotherapy were associated with a significantly decreased risk of PTB compared with ART-naive WLHIV (RR 0.70, 95% CI 0.62–0.79) (Table 3a, Appendix, p. 30, http://links.lww.com/QAD/C513). Heterogeneity was moderate (I^2 66.4%) (Appendix, p. 30, http://links.lww.com/QAD/C513), and significance was retained in subgroup analyses for studies conducted in HICs (0.77, 0.70–0.84) and LMICs (0.65, 0.45–0.92) (Table 3b). There was no significant risk of PTB associated with WLHIV receiving monotherapy compared with HIV-negative women.

Twenty studies including 33 837 women showed no significant association with risk of PTB in WLHIV receiving HAART compared with ART-naive WLHIV (0.85, 0.66–1.10) (Table 3a, Appendix, p. 36, http://links.lww.com/QAD/C513). In the analysis containing 25 studies and 138 223 women, WLHIV receiving HAART were associated with increased risk of PTB compared with HIV-negative women (1.55, 1.38–1.74). Heterogeneity was high (I^2 87.4%) (Appendix, p. 36, http://links.lww.com/QAD/C513) but there was no evidence of publication bias (Peters' test, $P = 0.156$). The significance of this association was preserved in subgroup analyses of studies conducted in HICs (1.92, 1.51–2.43) and in LMICs (1.33, 1.21–1.45) (Table 3b).

There was no significant association with VPTB and WLHIV receiving monotherapy compared with ART-naive WLHIV (Table 3a, Appendix, p. 31, http://links.lww.com/QAD/C513). Additionally, no significant association was found between VPTB and WLHIV receiving HAART compared with ART-naive WLHIV (Table 3a, Appendix, p. 36, http://links.lww.com/QAD/C513), or WLHIV receiving HAART compared with HIV-negative women (Table 3a, Appendix, p. 41, http://links.lww.com/QAD/C513).

No studies containing WLHIV receiving monotherapy reported outcome data on sPTB. WLHIV receiving HAART were found to be associated with a significantly decreased risk of sPTB compared with ART-naive WLHIV (0.46, 0.32–0.67) (Table 3a, Appendix, p. 37, http://links.lww.com/QAD/C513), whereas WLHIV receiving HAART were associated with a significantly increased risk of sPTB compared with HIV-negative women (2.10, 1.48–2.96) (Table 3a, Appendix, p. 41, http://links.lww.com/QAD/C513).

In the analysis of 12 studies containing 40 495 women, WLHIV receiving monotherapy were at significantly decreased risk of LBW (0.77, 0.67–0.88) compared with ART-naive WLHIV (Table 3a, Appendix, p. 31, http://links.lww.com/QAD/C513). Heterogeneity was moderate (I^2 68.1%) (Appendix, p. 31, http://links.lww.com/QAD/C513), and the association was retained in subgroup analyses for studies conducted in HICs (0.85, 0.78–0.93) and LMICs (0.73, 0.59–0.91) (Table 3b). No significant association with LBW was found in the comparison between WLHIV receiving monotherapy and HIV-negative women (Table 3a, Appendix, p. 34, http://links.lww.com/QAD/C513).

No significant association with LBW was found in the analysis of WLHIV receiving HAART compared with ART-naive WLHIV (Table 3a, Appendix. P. 37, http://links.lww.com/QAD/C513). However, there was a significantly increased risk of LBW associated with WLHIV receiving HAART compared with HIV-negative women in an analysis containing 15 studies and 207 857 women (1.79, 1.51–2.13) (Table 3a, Appendix, p. 42, http://links.lww.com/QAD/C513). There was a high level of heterogeneity (I^2 90.6%) (Appendix, p. 42, http://links.lww.com/QAD/C513) but there was no evidence of publication bias (Peters' test, $P = 0.433$). This significant association was retained in subgroup analyses for studies conducted in HICs (2.49, 1.56–3.98) and LMICs (1.56, 1.35–1.80) (Table 3b).

No significant association with VLBW was found for WLHIV receiving monotherapy compared with ART-naive WLHIV (Table 3a, Appendix, p. 32, http://links.lww.com/QAD/C513). One study, containing 1228 women, found a significantly decreased risk of VLBW associated with WLHIV receiving HAART compared with ART-naive WLHIV (0.36, 0.16–0.78) (Table 3a, Appendix, p. 38, http://links.lww.com/QAD/C513). There was no association with VLBW in WLHIV receiving HAART compared with HIV-negative women (Table 3a, Appendix. p. 42, http://links.lww.com/QAD/C513).

The analysis of three studies, containing 2161 women, showed that WLHIV receiving HAART were associated with a significantly increased risk of term LBW compared with HIV-negative women (1.88, 1.23–2.85) (Table 3a, Appendix, p. 43, http://links.lww.com/QAD/C513). This significance was retained in subgroup analyses of studies conducted in HICs, but not LMICs (Table 3b).

One study, including 1299 women, reported no significant association with preterm LBW in WLHIV receiving HAART compared with HIV-negative women (Table 3a, Appendix, p. 43, http://links.lww.com/QAD/C513).

In the analysis of four studies including 4681 women, WLHIV receiving monotherapy were not associated with SGA compared with ART-naive WLHIV (Table 3a,

Table 2. Antiretroviral therapies, HIV/antiretroviral therapy comparisons, and perinatal outcomes reported by studies included in the systematic review and meta-analysis.

Study: first author (year) [ref]	ART regimens	WLHIV with monotherapy vs. ART-naive WLHIV	WLHIV with monotherapy vs. HIV-negative women	WLHIV with HAART vs. ART-naive WLHIV	WLHIV with HAART vs. HIV-negative women	Perinatal outcomes
Ai-Jie (2013) [26]	77.4% ZDV monotherapy, 22.6% NNRTI-based HAART (ZDV-3TC-NVP)	Yes	No	Yes	No	LBW
Albert (2020) [27]	4.5% mono/dual/triple NRTI therapy, 17.7% NNRTI-based HAART, 73.7% PI-based HAART, 4.1% INSTI-based HAART	No	No	Yes	No	sPTB
Azria (2009) [28]	PI-based HAART (LPV/r)	No	No	No	Yes	PTB, VPTB, SGA, VSGA, NND
Bailey (2013) [29]	91.3% ZDV monotherapy, 1.2% dual therapy, 7.5% HAART (91% PI-based HAART)	Yes	No	Yes	No	PTB
Balogun (2018) [30]	PI-based HAART (50.7% LPV/r, 31.8% ATV/r, 4.8% DRV/r)	No	No	No	Yes	sPTB, SGA
Bengtson (2020) [31]	NNRTI-based HAART (TDF-FTC/3TC-EFV)	No	No	No	Yes	PTB, SGA, VSGA
Boer (2006) [32]	PI-/NNRTI-based HAART (proportion unspecified)	No	No	No	Yes	PTB, LBW, VLBW
Boyajian (2012) [33]	75% PI-based HAART, 25% non-PI based HAART	No	No	No	Yes	PTB, LBW, SGA
Carceller (2009) [34]	85.4% PI-based HAART, 14.6% non-PI based HAART	No	No	No	Yes	PTB, Term LBW
Chagomerana (2017) [35]	NNRTI-based HAART (TDF-3TC-EFV)	No	No	Yes	No	PTB, VPTB
Chen (2012) [36]	58.4% ZDV monotherapy, 2.9% PI-based HAART (LPV/r-ZDV-3TC), 33.5% NNRTI-based HAART (NVP-ZDV-3TC), 5.2% unspecified HAART	No	Yes	No	Yes	PTB, SGA
Chibwesha (2016) [37]	66.6% ZDV monotherapy, 33.4% HAART [unspecified drug class(es)]	Yes	Yes	Yes	Yes	LBW
Cooper (2002) [38]	62% ZDV monotherapy, 16.2% dual therapy (96.8% two NRTIs, 2.2% NRTI-NNRTI, 0.5% two NNRTIs), 21.8% HAART (NNRTI-based, PI-based, or NNRTI-PI-based)	Yes	No	Yes	No	PTB, LBW
Cotter (2006) [39]	49.3% ZDV monotherapy, 37.3% non-PI-based HAART, 13.4% PI-based HAART	Yes	No	No	No	LBW, VLBW
Dadabhai (2019) [40]	NNRTI-based HAART (TDF-3TC-EFV)	No	No	No	Yes	PTB, LBW, Term LBW, Preterm LBW, SGA, VSGA
De Souza (2000) [41]	ZDV monotherapy	Yes	No	No	No	PTB
Garcia-Otero (2019) [42]	HAART (29.8% NNRTI-containing, 66% PI-containing, 14.9% INSTI-containing)	No	No	No	Yes	PTB, SGA, NND
Goetghebuer (2019) [43]	77.3% PI-based HAART, 12.9% NNRTI-based HAART, 5.3% NRTI-based HAART, 4.5% other regimen	No	No	No	Yes	PTB, LBW
Haeri (2009) [44]	HAART (94% NRTI-containing, 20% NNRTI-containing, 74% PI-containing)	No	No	No	Yes	PTB, sPTB, Term LBW, SGA
Hernandez (2017) [45]	4.2% ZDV monotherapy, 33.3% NNRTI-based HAART, 58.3% PI-based HAART, 4.2% NRTI-based HAART	No	No	No	Yes	SGA
Hu (2019) [46]	20.1% ZDV monotherapy/ZDV-3TC dual therapy, 79.9% HAART (NNRTI-based/PI-based)	No	No	Yes	No	PTB, SGA
Joseph (2011) [47]	NNRTI-based HAART (NVP)	No	No	Yes	No	LBW

Table 2 (*continued*)

Study: first author (year) [ref]	ART regimens	WLHIV with monotherapy vs. ART-naive WLHIV	WLHIV with monotherapy vs. HIV-negative women	WLHIV with HAART vs. ART-naive WLHIV	WLHIV with HAART vs. HIV-negative women	Perinatal outcomes
Jumare (2019) [48]	HAART [drug class(es) unspecified]	No	No	No	Yes	LBW
Kakkar (2015) [49]	16.8% ZDV monotherapy, 14.5% NRTI-/NNRTI-containing dual therapy/ HAART, 68.7% PI-based HAART	Yes	No	Yes	No	PTB
Kowalska (2003) [50]	43.2% ZDV monotherapy, 22.2% PI-based HAART, 34.6% non-PI-based HAART	Yes	No	Yes	No	PTB, LBW
Li (2016) [13]	61.8% ZDV monotherapy, 35.5% NNRTI-based HAART, 0.6% PI-based HAART, 2.1% unspecified HAART	Yes	No	Yes	No	PTB, LBW, SGA, VSGA
Li (2020) [51]	24.2% mono/dual therapy, 75.8% HAART (drug class(es) unspecified)	No	No	Yes	Yes	PTB, LBW, SGA
Liff (2020) [52]	78% NNRTI-based HAART, 12% INSTI-based HAART, 10% other HAART	No	No	No	Yes	PTB
Lopez (2012) [53]	HAART (98.7% NRTI-containing, 51.3% NNRTI-containing, 59.7% PI-containing)	No	No	No	Yes	PTB, sPTB
Malaba (2017) [54]	71.6% NNRTI-based HAART, 2.3% PI-based HAART, 26.1% other HAART	No	No	No	Yes	PTB, VPTB, LBW, VLBW, SGA
Malaba (2018) [55]	92.5% NNRTI-based HAART, 2.8% PI-based HAART, 4.7% other HAART	No	No	No	Yes	PTB, SGA
Mandelbrot (1998) [56]	ZDV monotherapy	Yes	No	No	No	PTB
Marazzi (2011) [57]	NRTI-/NNRTI-based HAART (proportion unspecified)	No	No	Yes	No	PTB
Marti (2007) [58]	15.1% ZDV monotherapy, 13.8% NRTI dual therapy, 7.9% NNRTI-based HAART, 61.8% PI-based HAART, 1.4% NRTI-based HAART	Yes	No	Yes	No	PTB, LBW
Matheson (1995) [59]	ZDV monotherapy	Yes	No	No	No	PTB
Mehta (2019) [60]	98% NNRTI-based HAART, 0.9% PI-based HAART, 1.1% unspecified HAART	No	No	No	Yes	PTB, LBW, SGA, NND
Moodley (2016) [61]	27.5% ZDV monotherapy, 72.5% NNRTI-based HAART	Yes	Yes	Yes	Yes	PTB, LBW, SGA
Moseholm (2019) [62]	13.6% NNRTI-based HAART, 78.4% PI-based HAART, 5.7% NRTI-based HAART, 2.3% unspecified HAART	No	No	No	Yes	PTB
Olagbuji (2010) [63]	NNRTI-based HAART (ZDV/ 3TC/NVP)	No	No	No	Yes	LBW
Phiri (2015) [64]	20% ZDV monotherapy, 15.3% NRTI-NNRTI dual therapy, 21.3% NRTI dual therapy/ HAART, 43.4% PI-based therapy (unspecified regimen complexity)	Yes	No	No	No	PTB, SGA
Ramokolo (2017) [65]	38.5% ZDV monotherapy, 61.5% NNRTI-based HAART (TDF-3TC/FTC-NVP)	Yes	Yes	Yes	Yes	PTB, LBW, SGA
Rempis (2017) [66]	NNRTI-based HAART (TDF-3TC-EFV)	No	No	No	Yes	SGA
Rudin (2011) [67]	26.4% ZDV mono/dual therapy, 61.8% PI-based HAART, 11.8% non-PI-based HAART	No	No	Yes	No	PTB, VPTB
Santosa (2019) [68]	1.6% ZDV monotherapy, 96% HAART, 2.4% unspecified regimen	No	No	No	Yes	PTB, VPTB, LBW, VLBW, SGA, VSGA, Stillbirth, NND
Saums (2019) [69]	10.9% NNRTI-based HAART, 54.7% PI-based HAART, 34.3% INSTI-based HAART	No	No	No	Yes	PTB

Table 2 (*continued*)

Study: first author (year) [ref]	ART regimens	WLHIV with monotherapy vs. ART-naive WLHIV	WLHIV with monotherapy vs. HIV-negative women	WLHIV with HAART vs. ART-naive WLHIV	WLHIV with HAART vs. HIV-negative women	Perinatal outcomes
Schulte (2007) [70]	42.1% ZDV monotherapy, 16.7% dual therapy, 12.6% PI-based HAART, 28.6% non-PI-based HAART	Yes	No	Yes	No	PTB, LBW
Sebitloane (2017) [71]	36.6% ZDV monotherapy, 63.4% NNRTI-based HAART	No	Yes	No	Yes	PTB
Short (2014) [72]	20.1% ZDV monotherapy, 2.2% NRTI dual therapy, 42.4% NNRTI-based HAART, 29.8% PI-based HAART, 1.5% NRTI-based HAART, 4% unspecified HAART	Yes	No	Yes	No	PTB
Silverman (2010) [73]	PI-based HAART (ZDV-3TC-LPV/r)	No	No	Yes	No	LBW
Simonds (1998) [74]	ZDV monotherapy	Yes	No	No	No	PTB, LBW
Snijdewind (2018) [75]	31.5% NNRTI-based HAART, 66.7% PI-based HAART, 1.8% other HAART	No	No	No	Yes	PTB, VPTB, LBW, VLBW, SGA
Tiam (2019) [76]	96.5% NNRTI-based HAART, 2.3% other HAART, 2.2% no ART	No	No	No	Yes	PTB, LBW, VLBW
Townsend ECS (2010) [18]	27.8% ZDV monotherapy, 11.8% NRTI dual therapy, 36.2% PI-based HAART, 24.2% non-PI-based HAART	Yes	No	Yes	No	PTB
Townsend NSHPC (2010) [18]	16.3% ZDV monotherapy, 3.2% dual therapy, 42% PI-based HAART, 38.5% non-PI-based HAART	Yes	No	Yes	No	PTB
Tuomala (2002) [19]	74.8% ZDV monotherapy, 6.5% PI-based dual/HAART, 18.7% non-PI-based dual/HAART	Yes	No	No	No	PTB, VPTB, LBW, VLBW
Van der Merwe (2011) [77]	42.8% NNRTI-based HAART, 44.5% PI-based HAART, 12.7% unspecified HAART	No	No	Yes	No	PTB, LBW, VLBW
Von Linstow (2010) [78]	12.1% ZDV monotherapy/dual therapy, 87.9% NNRTI-/PI-based HAART	No	No	Yes	No	LBW
Watts (2013) [79]	7.6% mono/dual therapy, 8.8% NNRTI-based HAART, 72.9% PI-based HAART, 10.7% NRTI-based HAART	No	No	Yes	No	PTB, sPTB
Yu (2012) [80]	NNRTI-based HAART	No	No	Yes	No	PTB, LBW
Zash (2018) [81]	72.7% NNRTI-based HAART (TDF-FTC-EFV), 27.3% INSTI-based HAART (TDF-FTC-DTG)	No	No	No	Yes	PTB, VPTB, SGA, VSGA, NND
Ziske (2013) [82]	ZDV monotherapy	Yes	No	No	No	PTB

3TC, lamivudine; ART, antiretroviral therapy; ATV/r, ritonavir-boosted atazanavir; cART, combination antiretroviral therapy (≥2 antiretroviral drugs); DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; HAART, highly active antiretroviral therapy (at least three antiretroviral drugs); INSTI, integrase strand transfer inhibitor; LBW, low birthweight; LPV/r, ritonavir-boosted lopinavir; NND, neonatal death; NNRTI, nonnucleoside transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous preterm birth; TDF, tenofovir disoproxil fumarate; VLBW, very low birthweight; VPTB, very preterm birth; VSGA, very small for gestational age; WLHIV, women living with HIV; ZDV, zidovudine.

Appendix, p.32, http://links.lww.com/QAD/C513). Three studies, conducted in LMICs, including 40 057 women, found a significantly increased risk of SGA associated with WLHIV receiving monotherapy compared with HIV-negative women (1.16, 1.04–1.30) (Table 3a, Appendix, p. 35, http://links.lww.com/QAD/C513).

In the analysis of five studies with 6818 women conducted in LMICs, WLHIV receiving HAART were associated with a significantly increased risk of SGA compared with ART-naive WLHIV (1.38, 1.09–1.75) (Table 3a, Appendix, p. 38, http://links.lww.com/QAD/C513). In an analysis of 19 studies and 127 032 women, WLHIV receiving HAART were also at significantly increased risk of SGA compared with HIV-negative women (1.80, 1.34–2.40) (Table 3a, Appendix, p. 44,

Table 3. Perinatal outcomes associated with women living with HIV receiving HAART or monotherapy compared to antiretroviral therapy-naive women living with HIV and HIV-negative women.

(a) All studies

	Perinatal outcomes										
	PTB	**VPTB**	**sPTB**	**LBW**	**VLBW**	**Term LBW**	**Preterm LBW**	**SGA**	**VSGA**	**Stillbirth**	**NND**
	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
WLHIV with monotherapy vs ART-naïve WLHIV	0.70 (0.62, 0.79)	0.96 (0.63, 1.47)		0.77 (0.67, 0.88)	0.63 (0.24, 1.64)			1.08 (0.90, 1.29)	1.43 (0.97, 2.10)		
WLHIV with monotherapy vs HIV-negative women	1.04 (0.84, 1.29)			1.08 (0.88, 1.33)				1.16 (1.04, 1.30)			
WLHIV with HAART vs ART-naïve WLHIV	0.85 (0.66, 1.10)	0.89 (0.23, 3.51)	0.46 (0.32, 0.67)	0.92 (0.79, 1.08)	0.36 (0.16, 0.78)			1.38 (1.09, 1.75)	2.35 (1.60, 3.46)		
WLHIV with HAART vs HIV-negative women	1.55 (1.38, 1.74)	1.72 (0.75, 3.96)	2.10 (1.48, 2.96)	1.79 (1.51, 2.13)	1.70 (0.63, 4.57)	1.88 (1.23, 2.85)	1.17 (0.64, 2.14)	1.80 (1.34, 2.40)	1.22 (1.10, 1.34)	0.88 (0.34, 2.32)	1.27 (0.75, 2.15)

(b) Subgroup analysis by country income status

WLHIV with monotherapy vs ART-naïve WLHIV	**High income countries**	0.77 (0.70, 0.84)	0.96 (0.63, 1.47)		0.85 (0.78, 0.93)	0.63 (0.24, 1.64)			0.91 (0.55, 1.51)			
	Low- and middle-income countries	0.65 (0.45, 0.92)			0.73 (0.59, 0.91)				1.08 (0.86, 1.36)	1.43 (0.97, 2.10)		
WLHIV with monotherapy vs HIV-negative women	**High income countries**											
	Low- and middle-income countries	1.04 (0.84, 1.29)			1.08 (0.88, 1.33)				1.16 (1.04, 1.30)			
WLHIV with HAART vs ART-naïve WLHIV	**High income countries**	0.99 (0.79, 1.24)	1.86 (0.78, 4.46)	0.46 (0.32, 0.67)	0.79 (0.72, 0.87)	0.36 (0.16, 0.78)						
	Low- and middle-income countries	0.73 (0.48, 1.09)	0.47 (0.29, 0.77)		1.01 (0.78, 1.30)				1.38 (1.09, 1.75)	2.35 (1.60, 3.46)		
WLHIV with HAART vs HIV-negative women	**High income countries**	1.92 (1.51, 2.43)	2.12 (0.38, 12.04)	2.09 (1.48, 2.96)	2.49 (1.56, 3.98)	1.84 (0.14, 23.58)	1.91 (1.10, 3.29)		3.78 (1.29, 11.08)	1.20 (0.29, 4.92)		0.40 (0.02, 8.21)
	Low- and middle-income countries	1.33 (1.21, 1.45)	1.11 (0.82, 1.49)		1.56 (1.35, 1.80)	1.38 (0.77, 2.45)	1.83 (0.95, 3.53)	1.17 (0.64, 2.14)	1.41 (1.16, 1.72)	1.22 (1.10, 1.34)	0.88 (0.34, 2.32)	1.34 (0.76, 2.35)

Relative risk (RR) and 95% confidence interval (95% CI) of random-effects meta-analyses. For forest plots see Appendix, pp. 30–45, http://links.lww.com/QAD/C513. RR greater than 1 indicates that women living with HIV receiving ART are associated with an increased risk of the corresponding perinatal outcome. ART, antiretroviral therapy; LBW, low birthweight; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous preterm birth; VLBW, very low birthweight; VPTB, very preterm birth; VSGA, very small for gestational age; WLHIV, women living with HIV.

http://links.lww.com/QAD/C513). There was a high level of heterogeneity (I^2 97.6%) (Appendix, p. 44, http://links.lww.com/QAD/C513), but the Peters' test showed no evidence of publication bias ($P = 0.803$). Additionally, the significant association was retained in subgroup analyses of studies conducted in HICs (3.78, 1.29–11.08) and LMICs (1.41,1.16–1.72) (Table 3b).

A single study reported no significant association with VSGA in WLHIV receiving monotherapy compared with ART-naive WLHIV (Table 3a, Appendix, p. 33, http://links.lww.com/QAD/C513). A single study reported an increased risk of VSGA in WLHIV receiving HAART compared with ART-naive WLHIV (2.35, 1.60–3.46) (Table 3a, Appendix, p. 39, http://links.lww.com/QAD/C513). In the analysis of five studies containing 59 746 women, WLHIV receiving HAART were found to be associated with a significantly increased risk of VSGA compared with HIV-negative women (1.22,1.10–1.34) (Table 3a, Appendix, p. 44, http://links.lww.com/QAD/C513). This association was retained in subgroup analysis of four studies with 59 446 women conducted in LMICs (1.22,1.10–1.34), but not HICs (Table 3b).

Only one study, containing 633 women, reported on stillbirth, finding no significant association in WLHIV receiving HAART compared with HIV-negative women (Table 3a, Appendix, p. 45, http://links.lww.com/QAD/C513).

Five studies, reporting on 67 665 women, were included in the analysis of NND in WLHIV receiving HAART compared with HIV-negative women, finding no significant association (Table 3a, Appendix, p. 45, http://links.lww.com/QAD/C513).

Discussion

This meta-analysis shows that WLHIV receiving ZDV monotherapy are at decreased risk of PTB and LBW, and comparable risk of SGA, compared with ART-naive WLHIV. WLHIV receiving ZDV monotherapy are at comparable risk of PTB and LBW, and an increased risk of SGA compared with HIV-negative women. In contrast, WLHIV receiving HAART are at comparable risk of PTB and LBW, and at increased risk of SGA, compared with ART-naive WLHIV. Importantly, WLHIV receiving HAART are at increased risk of PTB, sPTB, LBW, term LBW, SGA, and VSGA compared with HIV-negative women.

This study has several strengths. It is the largest study to date, assessing a comprehensive range of 11 perinatal outcomes in WLHIV receiving HAART or ZDV monotherapy, including 409 781 women from 61 studies. The analyses of PTB, LBW and SGA for the comparison between WLHIV receiving HAART and HIV-negative women were each supported by at least 15 studies and at least 127 000 pregnant women, providing strong evidence for the significant associations found. Outcomes and exposures were clearly predefined to minimize misclassification bias and promote consistency across studies. Subgroup and sensitivity analyses supported our main findings. The vast majority of women analysed resided in LMICs, where most WLHIV live, lending external validity to our findings.

This study has some limitations. All studies included are observational, and are therefore associated with a risk of bias. However, adjustment for covariates by regression analysis rarely resulted in a change in the significance of the effect estimate in individual studies. Nevertheless, we cannot exclude residual confounding. RCTs reported an increased risk of adverse perinatal outcomes associated with several HAART regimens compared with ZDV monotherapy [16]. However, few RCTs of ART in pregnancy have been conducted, they enrolled limited numbers of women, and ART was initiated during the second half of pregnancy, thereby limiting exposure to ART and detection of perinatal outcomes [16]. There were few studies in our analysis reporting on VPTB, sPTB, VLBW, term LBW, preterm LBW, VSGA, stillbirth, and NND. Nineteen studies did not report a method to assess gestational age, whereas only four studies used a first trimester ultrasound, the most accurate method to assess gestational age [83]. Certain perinatal outcomes, such as PTB and SGA, may therefore, have been vulnerable to misclassification bias because of inaccurate assessment of gestational age. In addition, differences in populations and settings between studies may have contributed to the heterogeneity observed in our analyses. Although prevalence of risk factors for adverse pregnancy outcomes differed between HICs and LMICs, findings were largely consistent between HICs and LMICs, in particular for the well supported findings for PTB, LBW, and SGA. Finally, patients included in our analyses were recruited over a relatively long time period. On average, WLHIV without ART were from earlier years, WLHIV receiving monotherapy from more recent years, and WLHIV receiving HAART from the most recent years. Temporal changes in risk factors and obstetric care might have created a chronological bias in the outcomes observed for the different treatment groups of WLHIV. Year of delivery was adjusted for in a number of included studies. However, if a temporal trend of improving obstetric care and outcomes exists, it is at odds with the finding that WLHIV receiving HAART have worse perinatal outcomes than WLHIV receiving monotherapy.

We included studies reporting on WLHIV receiving any HAART regimen or ZDV monotherapy to capture the overall effect of ART on adverse perinatal outcomes in

WLHIV as ART use in pregnancy was introduced. However, as WHO guidance changed, indications, timings of initiation, and drug regimens of ART used in pregnant WLHIV changed too [10,84]. Although prevention of vertical HIV transmission was the primary indication initially, this has been replaced by a policy of universal treatment. Preconception initiation of ART has been associated with an increased risk of adverse perinatal outcomes compared with ART initiation during pregnancy, although this is disputed by others [85,86]. The evidence on the association of different HAART regimens with perinatal outcomes is conflicting [12,87]. HAART regimes containing a protease inhibitor are associated with an increased risk of PTB in multiple studies [14–16], but not in others [88]. WHO guidance currently recommends dolutegravir (DTG)-containing HAART as the preferred first-line therapy [84]. A retrospective cohort study reported that perinatal outcomes were comparable between WLHIV receiving DTG-based and efavirenz (EFV)-based HAART [81,89]. However, a recent RCT reported that a regimen initiated during pregnancy containing DTG, emtricitabine (FTC), and tenofovir alafenamide fumarate (TAF) had the lowest rate of adverse pregnancy outcomes, compared with DTG/FTC/tenofovir disoproxil fumarate (TDF) and EFV/FTC/TDF [90].

The biological mechanisms contributing to the associations between HIV, ART, and adverse perinatal outcomes remain unclear [91]. Current evidence indicates that perinatal outcomes of ART-naive WLHIV are higher than HIV-negative women [2], perinatal outcomes in WLHIV receiving HAART remain higher than HIV-negative women, and WLHIV receiving ZDV monotherapy have similar outcomes (bar SGA) as HIV-negative women. The estimated effect sizes for PTB (1.55, 1.38–1.74), LBW (1.79, 1.51–2.13), and SGA (1.80, 1.34–2.40) in our comparison of WLHIV receiving HAART with HIV-negative women (Table 3a) are comparable with those reported for ART-naive WLHIV compared with HIV-negative women for PTB (1.63, 1.37–1.93), LBW (1.75, 1.52–2.02), and SGA (1.64, 1.29–2.09) [2], confirming the lack of beneficial impact of HAART on these perinatal outcomes. HIV infection is associated with $CD4^+$ depletion and chronic immune activation [92]. 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 HAART, and may be associated with increased risk of adverse perinatal outcomes [93,94]. WLHIV receiving HAART were reported to have distinct systemic cytokine profiles throughout pregnancy, compared with HIV-negative women, which may be associated with SGA [95]. Additionally, protease inhibitors included in HAART regimens may inhibit progesterone production by the placenta [96], and reduced progesterone levels were associated with increased risk of SGA [97]. Interestingly, a recent RCT of progesterone supplementation in pregnant WLHIV on ART (mostly NNRTI-ART) showed a reduction in VSGA [98].

Lifelong HAART provides significant benefits over antenatal ZDV monotherapy by reducing maternal morbidity and mortality, reducing horizontal HIV transmission, and protection of future pregnancies. However, it is concerning that WLHIV receiving HAART are associated with increased risks of a wide range of perinatal outcomes, especially as the proportion of pregnant WLHIV receiving HAART increases globally. It is crucial to determine the perinatal outcomes associated with different HAART regimens to determine the optimal HAART regimen(s) to minimize adverse perinatal outcomes. Further studies are urgently needed to elucidate the mechanism underlying adverse perinatal outcomes and develop preventive and therapeutic interventions to improve perinatal outcomes in WLHIV.

Acknowledgements

Systematic review registration number: CRD42021248987.

Author contributions: C.P., H.S., M.K., Z.B., and B.J. screened the literature search results for relevant manuscripts and assessed their eligibility, extracted data and conducted methodological quality assessments. C.M. selected relevant studies and conducted meta-analyses. C. P. selected relevant studies and conducted the meta-analyses, subgroup and sensitivity analyses, interpreted the data and wrote the first draft of the manuscript. S.K. designed and conducted the literature search. J.H. conceived, designed and coordinated the study, developed the systematic review protocol, assisted with the literature search, assessment of eligibility of manuscripts, data extraction, methodological quality assessment, designed the meta-analysis plan, interpreted the data and wrote the manuscript. J.H. 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.

Conflicts of interest

There are no conflicts of interest.

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