

Title

Perinatal outcomes associated with combination antiretroviral therapy compared to monotherapy: systematic review and meta-analysis

Running head

Perinatal outcomes associated with cART

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Abstract

Objectives

Increasing numbers of women living with HIV (WLHIV) worldwide receive combination antiretroviral therapy (cART) during pregnancy. We aimed to assess the risk of adverse perinatal outcomes in pregnant WLHIV receiving cART compared to pregnant WLHIV receiving zidovudine monotherapy.

Design

Systematic review and meta-analysis.

Methods

We searched four electronic literature databases (PubMed, CINAHL, Global Health, EMBASE) for studies published between 01/01/1980-20/04/2020 using a comprehensive search strategy. Studies reporting data on WLHIV receiving cART compared to WLHIV receiving monotherapy for 11 adverse perinatal outcomes were sought: preterm birth (PTB), very PTB, spontaneous PTB, low birthweight (LBW), very LBW, preterm and term LBW, small for gestational age (SGA), very SGA (VSGA), stillbirth, and neonatal death. Random-effects meta-analyses were conducted to calculate relative risk (RR) and 95% confidence intervals (95% CI).

Results

We included 30 studies reporting on 317,101 women in 27 countries. WLHIV receiving cART were at increased risk of PTB (RR 1.32, 95%CI 1.18-1.46), LBW (1.35, 1.19-1.53), SGA (1.32, 1.13-1.53), VSGA (1.64, 1.34-2.02), and stillbirth (2.41, 1.83-3.17) compared to WLHIV

receiving monotherapy. The significance of these results was maintained in subgroup analyses for studies conducted in low-and-middle-income countries and average quality studies. Additionally, WLHIV receiving non-nucleoside reverse transcriptase inhibitor-based cART were associated with increased risk of PTB, LBW, and stillbirth, while WLHIV receiving protease inhibitor-based cART were associated with increased risk of PTB, compared to WLHIV receiving monotherapy.

Conclusion

Pregnant WLHIV receiving cART are associated with increased risk of adverse perinatal outcomes, compared to WLHIV receiving monotherapy.

Introduction

In 2020, 37.7 million people worldwide were living with HIV, including 19.3 million women of childbearing age[1]. An estimated 1.3 million women living with HIV (WLHIV) are pregnant each year, of whom the majority reside in sub-Saharan Africa[1]. Antiretroviral therapy (ART)-naïve maternal HIV infection is associated with an increased risk of preterm birth (PTB), low birthweight (LBW), small for gestational age (SGA) and stillbirth[2]. These adverse perinatal outcomes are significant contributors to childhood mortality and morbidity, with the highest rates found in sub-Saharan Africa[3–5]. Thus, understanding the association between WLHIV and adverse perinatal outcomes is important in addressing the United Nations' Sustainable Development Goal 3 (SDG3) target 3.2, which aims to reduce neonatal and under-5 mortality to 12 and 25 per 1,000 live births, respectively, by 2030[6].

ART is crucial to improve maternal health in WLHIV and to reduce vertical HIV transmission. In the past, the World Health Organisation (WHO) recommended zidovudine (ZDV) monotherapy to pregnant WLHIV to reduce the risk of vertical HIV transmission (Option A), while combination antiretroviral therapy (cART, i.e., triple drug therapy) was recommended for those WLHIV who required treatment for their own health as well as to reduce vertical HIV transmission (Option B)[7]. In 2013, this guidance was updated and all pregnant WLHIV were recommended to receive antenatal cART[8]. From 2015, the WHO recommended that cART should be initiated as soon as possible following diagnosis in all people with HIV, including pregnant WLHIV[9]. Following these changes, the proportion of pregnant WLHIV receiving ZDV monotherapy decreased from 31% to 0% in the period 2011-2020, while pregnant WLHIV receiving cART increased from 27% to 83%[1].

The impact of increasing numbers of pregnancies exposed to cART on important perinatal outcomes is unclear. Several studies suggest adverse perinatal outcomes are associated with ART exposure during pregnancy, with conflicting results regarding drug classes, timing of ART initiation, and regimen complexity[10–13]. A network meta-analysis of seven randomised controlled trials (RCTs) demonstrated that several antenatal cART regimens were associated with an increased risk of PTB, LBW, and very LBW compared to ZDV monotherapy[14]. Several cohort studies report an increased risk of PTB and LBW in pregnant WLHIV receiving cART, but not in WLHIV receiving ZDV monotherapy[15,16]. However, other studies report no significant association[17]. The same network meta-analysis of RCTs found that a protease inhibitor(PI)-based cART regimen was associated with increased risk of spontaneous PTB compared to a nucleoside reverse transcriptase inhibitor (NRTI)-based cART regimen, however no other significant associations were found among cART regimens[14]. In contrast, a meta-analysis of 34 cohort studies found that PI-cART was associated with a significantly increased risk of SGA and very SGA, but not PTB or any other perinatal outcomes, compared to non-PI-cART[18].

As ZDV monotherapy has been phased out and the number of pregnancies of WLHIV exposed to cART increases, it is important to understand whether cART and ZDV monotherapy impact perinatal outcomes differently. Therefore, we conducted a systematic review and meta-analysis of cohort studies examining the risk of 11 specific perinatal outcomes in WLHIV receiving cART compared to WLHIV receiving ZDV monotherapy.

Methods

Search strategy

The systematic review and meta-analyses were conducted as set out in a registered protocol (PROSPERO, number CRD42021248987), which was developed in line with the Cochrane guidelines. A comprehensive literature search strategy was developed by a specialist librarian (SK), and adapted to four electronic literature databases (PubMed, CINAHL (Ebscohost), Global Health (Ovid), EMBASE (Ovid)) to search for studies published between Jan 1, 1980 - April 20, 2020. Free text and controlled vocabulary search terms for ‘HIV’, ‘antiretroviral therapy’, ‘pregnancy outcome’, and ‘specific perinatal outcomes’ were used. The full search terms are included in Appendix pp2-14. Both full-texts and abstracts were considered, and no restrictions on methodology, country, or language were applied. Retrieved citations were imported into EndNote reference manager (EndNote X9; Clarivate Analytics, Philadelphia, Pennsylvania, USA) and deduplicated.

Study selection and eligibility criteria

Studies containing information on the association of pregnant women receiving cART or monotherapy (in distinct groups) with predefined adverse perinatal outcomes were eligible. Titles and abstracts of retrieved citations were reviewed. Full text manuscripts of selected citations were obtained and assessed by at least two independent investigators (CP, HS, MK, ZB, and BJ) against eligibility criteria. Inclusion criteria were study design (prospective and retrospective cohort studies), population (pregnant WLHIV), exposure (cART), and comparator (monotherapy) and adverse perinatal outcomes defined as follows: preterm birth (PTB, birth <37⁺⁰ weeks gestation);[19] very PTB (VPTB, birth <32⁺⁰ weeks gestation);[19] spontaneous PTB (sPTB, spontaneous birth <37⁺⁰ weeks gestation); low birthweight (LBW,

<2500g);[20] very LBW (VLBW, <1500g);[20] small for gestational age (SGA, birthweight for gestational age <10th centile) or very SGA (VSGA, birthweight for gestational age <3rd centile) according to the reference chart used at the study site,[21] stillbirth (delivery of an infant without any signs of life with birthweight \geq 1000 g or gestational age \geq 24⁺⁰ weeks or body length \geq 35 cm);[22] and neonatal death (NND, death of an infant in the first 28 days of life) [22]. Term and preterm LBW were defined according to definitions of PTB and LBW. Perinatal outcome data were not included if outcomes were undefined or not defined in line with our definitions. cART exposure was defined as receiving any combination of \geq 3 antiretroviral drugs. Monotherapy exposure was defined as receiving zidovudine (ZDV) during pregnancy. A single dose of nevirapine at birth or antenatal ART of duration <30 days were not considered ART exposure. If a cohort was reported more than once, the study that contained the most recent and complete data was included. If multiple studies reported different outcomes for the same cohort, each study was included. References of any included studies were assessed for additional studies. Any ambiguities were resolved with the senior investigator (JH). Details of excluded citations are available upon request.

Data extraction

At least two investigators (CP, HS, MK, ZB, and BJ) extracted data on study characteristics, ART exposures, and adverse perinatal outcomes from eligible studies. Details on methods used 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 ART exposure were also extracted. All data were reviewed by the senior investigator (JH).

Quality assessment

The quality of each study was assessed by at least two investigators (CP, HS, MK, ZB, and BJ) and reviewed by the senior investigator (JH) using an adapted Newcastle-Ottawa Scale [23]. Nine criteria were assessed over three domains: Selection of study participants (maximum 4 points), Comparability of groups (maximum 2 points), and Assessment of outcomes (maximum 3 points). Studies were defined as ‘good’, ‘average’, or ‘poor’ quality according to predefined criteria (Appendix pp15-21).

Statistical analysis

Relative risk (RR) and corresponding 95% confidence intervals (CIs) were used to assess the risk of perinatal outcomes in WLHIV receiving cART compared to WLHIV receiving monotherapy. If two or more studies reported data for the same perinatal outcome, 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 due to clinical and methodological variability between studies. Heterogeneity was classified as none (<25%), low (25-49%), moderate (50-74%), or high ($\geq 75\%$). Subgroup analyses were carried out to assess the effects of country income status and class of cART regimen, and sensitivity analyses were done to investigate whether study quality and the adjustment for confounders had an impact on the associations between ART exposure and perinatal outcomes. Publication bias was assessed using the Peters’ test where meta-analyses contained ten or more studies. All statistical analyses were done with Stata version 15 (College Station, Texas, USA). The systematic review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[24]

201 **Role of funding sources**

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

Results

Our search yielded 94,594 citations, of which 30 studies were included in the meta-analysis. The numbers of studies reporting each perinatal outcome for the comparison of WLHIV receiving cART with WLHIV receiving monotherapy are shown in Figure 1.

The characteristics of each included study are summarised in Table 1 [11,15–17,25–49]. 14 prospective (47%) and 16 retrospective (53%) cohort studies reported data from 317,101 women in 27 countries (Table 1). 20 studies (67%) including 278,784 women (88%) took place in low- and middle-income countries (LMICs), while 10 studies (32%) with 38,317 women (12%) took place in high income countries (HICs). 22 studies (73%) reported the methods used to determine gestational age, with only one study (3%) using first trimester ultrasound (Table 1). 22 studies (73%) used methods to assess potential confounding factors, including regression analysis, risk factor analysis, and matching (Table 1, Appendix pp22-24). Of the 18 analyses reported by individual studies that were adjusted for confounding factors, only 2 resulted in a change in the significance of the effect estimate (Appendix pp50-52). Quality assessments classified 17 studies (57%) as poor quality and 13 (43%) as average quality. No studies were classified as good quality (Table 1, Appendix pp18-21). A larger proportion of studies from LMICs were assessed as average quality (50% average, 50% poor) compared to studies from HICs (30% average, 70% poor).

The cART regimens received by WLHIV, the timing of cART initiation, and perinatal outcomes analysed for each study are summarised in Table 2. 12 studies (40%) reported outcome data for WLHIV receiving NNRTI-based cART, and 8 studies (25%) reported data for WLHIV receiving PI-based cART. 7 studies (23%) reported WLHIV receiving antenatal

cART, with the remainder reporting mixed antenatal/preconception (54%) or unspecified timing of cART initiation (23%)(Table 2).

Random-effects meta-analyses were conducted to compare perinatal outcomes in WLHIV receiving cART with WLHIV receiving ZDV monotherapy (Figure 2A, Appendix pp25-29). Subgroup analyses were carried out according to drug class of cART regimen (Figure 2B-C, Appendix pp30-34), country income status (Figure 3A-B, Appendix pp35-39), and study quality (Figure 3C-D, Appendix pp 40-45).

Preterm birth (PTB)

In the analysis of 24 studies containing 56,755 women, WLHIV receiving cART were associated with a significantly increased risk of PTB (RR 1.32, 95% CI 1.18-1.46) compared to WLHIV receiving monotherapy (Figure 2A, Appendix p25). Heterogeneity was high (I^2 78.6%), however no publication bias was detected (Peters' test, $p=0.462$). Significance was retained in the subgroup analysis containing 11 studies and 17,656 women comparing WLHIV receiving NNRTI-based cART and WLHIV receiving monotherapy (1.22, 1.06-1.40)(Figure 2B, Appendix p30). Heterogeneity was moderate (I^2 56.1%), and there was no evidence of publication bias (Peters' test, $p=0.454$). Similarly, in the subgroup analysis containing seven studies and 8619 women, WLHIV receiving PI-based cART were found to be associated with an increased risk of PTB compared to WLHIV receiving monotherapy (1.64, 1.08-2.50)(Figure 2C, Appendix p33).

Additionally, subgroup analyses by country income status and study quality showed that WLHIV receiving cART were associated with a significantly increased risk of PTB in LMICs (1.31, 1.14-1.50)(Figure 3B, Appendix p36), HICs (1.34, 1.11-1.61)(Figure 3A, Appendix

p35), average quality studies (1.43, 1.24-1.65)(Figure 3C, Appendix p40), and poor quality studies (1.21, 1.07, 1.36)(Figure 3D, Appendix p44).

Very PTB (VPTB)

A single average quality study, reporting on 2549 WLHIV in a LMIC, showed no significant increase in risk of VPTB in WLHIV receiving cART compared to WLHIV receiving monotherapy (1.39, 0.41-4.76)(Figure 2A, Appendix p26). All cART regimens in this cohort were NNRTI-based (Table 2, Figure 2B, Appendix p30).

Spontaneous PTB (sPTB)

One average quality study reported outcome data for sPTB, containing 166 women in a LMIC. No significant association for sPTB was found for WLHIV receiving cART compared to WLHIV receiving monotherapy (1.71, 0.79-3.68)(Figure 2A, Appendix p26). All cART regimens in this cohort were PI-based (Table 2, Figure 2C, Appendix p33).

Low birthweight (LBW)

18 studies, including 58,255 women, were included in the analysis that found WLHIV receiving cART were associated with an increased risk of LBW compared to WLHIV receiving monotherapy (1.35, 1.19-1.53)(Figure 2A, Appendix p27). There was a moderate level of heterogeneity (I^2 73.6%), and no significant publication bias (Peters' test, $p=0.841$). In the analysis of nine studies, including 11,817 women, a significantly increased risk of LBW was associated with WLHIV receiving NNRTI-based cART (1.42, 1.25-1.62)(Figure 2B, Appendix p31). Heterogeneity was low (I^2 12.2%). No significant association was seen in the analysis of WLHIV receiving PI-based cART compared to WLHIV receiving monotherapy (1.19, 0.74-1.91)(Figure 2C, Appendix p34), containing only four studies and 4085 women.

A significant association with LBW in WLHIV receiving cART compared to WLHIV receiving monotherapy was seen in subgroup analyses containing studies from LMICs (1.43, 1.31-1.57)(Figure 3B, Appendix p37), and both average (1.40, 1.25-1.57) and poor quality studies (1.30, 1.08-1.57)(Figure 3C-D, Appendix p41,p44). No significant association was seen in the analysis of four studies containing 6382 women that were conducted in HICs (0.96, 0.82-1.14)(Figure 3A, Appendix p35).

Term LBW

No significant association between term LBW and WLHIV receiving cART compared to WLHIV receiving monotherapy was found in a single average quality study reporting on 819 women from a LMIC (1.64, 0.93-2.91)(Figure 2A, Appendix p27).

Small for gestational age (SGA)

In the analysis of seven studies reporting on 24, 976 women in LMICs, a significantly increased risk of SGA was associated with WLHIV receiving cART compared to WLHIV receiving monotherapy (1.32, 1.13-1.53)(Figure 2A, Appendix p28). Heterogeneity was high (I^2 82.4%). No significant association was seen in subgroup analyses for WLHIV receiving NNRTI-based cART (1.16, 0.73-1.83)(Figure 2B, Appendix p31), or PI-based cART (1.02, 0.53-1.94)(Figure 2C, Appendix p34) compared to WLHIV receiving monotherapy. A significant association with SGA was found in subgroup analyses for average quality studies (1.35, 1.15-1.58) and poor quality studies (1.17, 1.01-1.36)(Figure 3C-D, Appendix p42,p45).

Very SGA (VSGA)

301 A single poor quality study including 2800 women in a LMIC reported that WLHIV receiving
302 cART are associated with an increased risk of VSGA compared to WLHIV receiving
303 monotherapy (1.64, 1.34-2.02)(Figure 2A, Appendix p28).

304

305 **Stillbirth**

306 One average quality study, reporting on 5091 women in a LMIC, found a significantly
307 increased risk of stillbirth associated with WLHIV receiving NNRTI-based cART compared
308 to WLHIV receiving monotherapy (2.41, 1.83-3.17)(Figure 2A&B, Appendix p29,p32).

309

Discussion

This meta-analysis shows that WLHIV receiving cART are associated with significantly increased risk of PTB, LBW, SGA, VSGA, and stillbirth compared to WLHIV receiving ZDV monotherapy. The significance of these results was maintained in subgroup analyses for studies conducted in low-and-middle-income countries and average-quality studies. Additionally, WLHIV receiving NNRTI-based cART were associated with increased risk of PTB, LBW, and stillbirth, while WLHIV receiving PI-based cART were associated with increased risk of PTB, compared to WLHIV receiving monotherapy.

This study has several strengths. It is the largest study to date, analysing 30 studies from 27 countries including 317,101 women reporting on a broad range of perinatal outcomes of WLHIV receiving cART compared to ZDV monotherapy. The analyses for PTB and LBW are supported by 24 and 18 studies respectively, including $\geq 55,000$ women each, providing strong evidence for the significant associations found. The majority of included pregnant WLHIV (88%) resided in LMICs, reflecting the real-world burden of maternal HIV. Exposures and outcomes were predefined to ensure consistency across studies and to minimise misclassification bias. A random-effects meta-analysis model was used to account for heterogeneity. Subgroup and sensitivity analyses for study quality and country income status supported our main findings. The Peters' test confirmed an absence of publication bias in analyses with ≥ 10 studies. The systematic review and meta-analysis were conducted according to the Cochrane and PRISMA guidelines.

There are some limitations to this study. All included studies are observational and therefore more vulnerable to risk of bias than RCTs. However, methods to correct for confounding

factors in each study were scrutinised. In studies that corrected for covariates using regression analyses, a change in effect estimate significance was rarely seen. Eight studies (26%) did not report a method to assess gestational age, while only one study used first trimester ultrasound, the most accurate method[50]. Outcomes such as PTB and SGA, which rely on accurate calculation of gestational age, may have been subject to misclassification bias. Additionally, few studies assessed VPTB, sPTB, Term LBW, VSGA and stillbirth, and no studies reported VLBW, preterm-LBW, and neonatal death. Differences in populations and settings may have contributed to the heterogeneity observed in our analyses. There may be a difference in the prevalence of risk factors for adverse perinatal outcomes between HICs and LMICs, although most included studies originated from LMICs.

Until 2013, many pregnant WLHIV in LMICs received ZDV monotherapy unless cART was indicated for their own health, suggesting those receiving ZDV monotherapy may have had overall better health[51]. Following updates in the WHO guidelines to a policy of universal treatment, the number of WLHIV receiving cART from preconception is increasing[9]. Consequently, WLHIV in our meta-analysis received a mixture of preconception and antenatal cART. Recent meta-analyses have demonstrated an increased risk of adverse perinatal outcomes with preconception ART; however, others dispute this [52–54]. We were unable to perform subgroup analyses of preconception and antenatal ART initiation as ZDV monotherapy was always initiated antenatally, and never preconception. The impact of different cART regimens on perinatal outcomes is conflicting, with some studies finding an increased risk of adverse perinatal outcomes associated with PI-based cART[12–14], but not others[55]. Our results indicate that WLHIV receiving either PI- or NNRTI-based cART remain at increased risk of PTB compared to monotherapy, in line with a recent meta-analysis finding no significant difference in the risk of PTB when comparing WLHIV receiving PI- and

non-PI-based ART[18]. WHO guidance currently recommends integrase inhibitor (INSTI)-based cART as first-line regimen[9]. Our analysis does not include any INSTI-based regimens due to the phasing out of ZDV monotherapy before the introduction of INSTIs, preventing direct comparison.

As cART is associated with superior viral suppression and improved maternal health, compared to monotherapy, our finding that cART is associated with poorer perinatal outcomes is surprising. The biological mechanisms underlying the association of HIV and ART exposure with adverse perinatal outcomes are unclear. Indeed, the aetiology of adverse perinatal outcomes is very complex and poorly understood, regardless of HIV infection[56]. HIV infection is associated with CD4 depletion and chronic immune activation[57]. Several immune cells, including innate lymphoid cells and mucosal associated invariant T cells, are depleted early in HIV infection, and do not recover after initiation of ART[58,59]. Reduced levels of these immune cells in WLHIV receiving cART are associated with an increased risk of PTB compared to HIV-negative women. WLHIV receiving ART are also found to have altered cytokine profiles compared to HIV-negative women, which may be associated with an increased risk of SGA[60]. It is not known whether cART is associated with different levels of these immune cells and mediators compared to ZDV monotherapy.

In studies conducted in mouse models and WLHIV, PI-based cART has been reported to alter placental vascular formation and is associated with decreased production of progesterone and increased risk of SGA compared to HIV-negative controls[61,62]. In line with this, progesterone supplementation was shown to reduce the risk of VSGA in pregnant WLHIV receiving ART (mostly NNRTI-based, 3% PI-based) in a recent RCT[63].

Despite the benefits of cART for maternal morbidity and mortality, and prevention of vertical transmission, it is concerning that cART is associated with increased risks of adverse perinatal outcomes compared to ZDV monotherapy. As ZDV monotherapy has been phased out, further studies are needed to determine the optimal cART regimens to minimise adverse perinatal outcomes. To overcome limitations in comparing outcomes between cART regimens between studies, the field would benefit from using internationally agreed standard definitions of adverse perinatal outcomes and accurate assessment of gestational age using first trimester ultrasound. Outcomes should be stratified by cART regimen, with details of each regimen, including time of initiation, provided. Data should be prospectively collected, including data on potential confounders, which should be corrected for in the analysis.

Recent randomised controlled trials of cART regimens initiated during pregnancy showed that dolutegravir-based cART had superior virological efficacy compared to efavirenz-based cART, and that a regimen containing dolutegravir, emtricitabine and tenofovir alafenamide fumarate had the lowest rate of adverse pregnancy outcomes.[64,65] Uncovering the mechanisms behind adverse perinatal outcomes would enable the development of preventative and therapeutic strategies to reduce adverse perinatal outcomes among WLHIV.

Contributors

CP, HS, MK, ZB, and BJ screened the literature search results for relevant manuscripts and assessed their eligibility, extracted data and conducted methodological quality assessments.

CP conducted the meta-analyses, 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, 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.

Data sharing statement

Study data are available on reasonable request to the corresponding author. The protocol for this review is available on the PROSPERO website (CRD42021248987).

Conflicts of interest

We declare that we have no conflicts of interest.

Legends

Figure 1. Study selection

* For example, women living with HIV were not pregnant. † For example, paper did not provide relevant outcome data. ‡ For example, Assisted Reproductive Technology (ART). Abbreviations: ART = antiretroviral therapy, cART= combination 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.

Figure 2. Perinatal outcomes associated with women living with HIV receiving cART, compared to women living with HIV receiving monotherapy.

Any cART (A.), NNRTI-based cART (B.) and PI-based cART (C.).

Relative risks, 95% confidence intervals, number of studies and women included in meta-analyses.

Abbreviations: 95% CI = 95% confidence interval, cART = combination antiretroviral therapy, LBW = low birthweight, NND = neonatal death, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PTB = preterm birth, RR = relative risk, 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.

Figure 3. Perinatal outcomes associated with women living with HIV receiving cART, compared to women living with HIV receiving monotherapy: subgroup analyses by country income status and study quality.

High income countries (A.) and low- and middle-income countries (B.), and average (C.) and poor (D.) quality studies. Relative risks, 95% confidence intervals, number of studies and women included in meta-analyses.

Abbreviations: 95% CI = 95% confidence interval, cART = combination antiretroviral therapy, LBW = low birthweight, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PTB = preterm birth, RR = relative risk, SGA = small for gestational age, sPTB = spontaneous preterm birth, VPTB = very preterm birth, 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.

* 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. Abbreviations: ART = antiretroviral therapy, IDU = illicit drug use, LNMP = last normal menstrual period.

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

Abbreviations: 3TC= lamivudine, cART= combination antiretroviral therapy (≥ 3 antiretroviral drugs), D4T= stavudine, EFV= efavirenz, FTC= emtricitabine, LBW= low birthweight, LPV/r= ritonavir-boosted lopinavir, NND= neonatal death, NNRTI= non-nucleoside transcriptase inhibitor, NRTI= nucleoside reverse transcriptase inhibitor, NVP= nevirapine, PI= protease inhibitor, PTB= preterm birth, SGA= small for gestational age, sPTB=

480 spontaneous preterm birth, TDF= tenofovir disoproxil fumarate, VLBW= very low
481 birthweight, VPTB= very preterm birth, VSGA= very small for gestational age, WLHIV =
482 women living with HIV, ZDV= zidovudine.

483

References

- 1 UNAIDS. Global AIDS Update: CONFRONTING INEQUALITIES, Lessons for pandemic responses from 40 years of AIDS. 2021.
- 2 Wedi COO, Kirtley S, Hopewell S, Corrigan R, Kennedy SH, Hemelaar J. **Perinatal outcomes associated with maternal HIV infection: A systematic review and meta-analysis.** *Lancet HIV* 2016; **3**:e33–e48.
- 3 Lee ACC, Kozuki N, Cousens S, Stevens GA, Blencowe H, Silveira MF, *et al.* **Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21 st standard: Analysis of CHERG datasets.** *BMJ (Online)* 2017; **358**. doi:10.1136/bmj.j3677
- 4 Lee ACC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al.* **National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010.** *Lancet Glob Health* 2013; **1**:e26–e36.
- 5 Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, *et al.* **Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis.** *Lancet Glob Health* 2019; **7**:e37–e46.
- 6 Transforming our world: the 2030 Agenda for Sustainable Development | Department of Economic and Social Affairs. <https://sdgs.un.org/2030agenda> (accessed 29 Dec2020).
- 7 World Health Organization (Geneva). *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infant: towards universal access: recommendations for a public health approach.* World Health Organization; 2006.
- 8 WHO | Guideline on when to start antiretroviral therapy and on preexposure prophylaxis for HIV. Geneva: World Health Organization; 2015.
- 9 **WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.** WHO Published Online First: 2018.<http://www.who.int/hiv/pub/arv/arv-2016/en/> (accessed 29 Dec2020).
- 10 Mofenson LM. Antiretroviral therapy and adverse pregnancy outcome: The elephant in the room? *Journal of Infectious Diseases*. 2016; **213**:1051–1054.
- 11 Li N, Sando MM, Spiegelman D, Hertzmark E, Liu E, Sando D, *et al.* **Antiretroviral therapy in relation to birth outcomes among HIV-infected women: A cohort study.** *Journal of Infectious Diseases* 2016; **213**:1057–1064.
- 12 Kourtis AP, Schmid CH, Jamieson DJ, Lau J. **Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: A meta-analysis.** *AIDS* 2007; **21**:607–615.
- 13 Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, *et al.* **Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy.** *Journal of Infectious Diseases* 2011; **204**:506–514.
- 14 Tshivuila-Matala COO, Honeyman S, Nesbitt C, Kirtley S, Kennedy SH, Hemelaar J. **Adverse perinatal outcomes associated with antiretroviral therapy regimens: systematic review and network meta-analysis.** *AIDS* 2020; **34**:1643–1656.
- 15 Ejigu Y, Magnus JH, Sundby J, Magnus MC. **Pregnancy outcome among HIV-infected women on different antiretroviral therapies in Ethiopia: A cohort study.** *BMJ Open* 2019; **9**:27344.

- 16 Townsend CL, Schulte J, Thorne C, Dominguez KL, Tookey PA, Cortina-Borja M, *et al.* **Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe.** *BJOG* 2010; **117**:1399–1410.
- 17 Cooper ER, Charurat M, Mofenson L, Hanson IC, Pitt J, Diaz C, *et al.* **Combination Antiretroviral Strategies for the Treatment of Pregnant HIV-1-Infected Women and Prevention of Perinatal HIV-1 Transmission.** *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2002; **29**:484–494.
- 18 Cowdell I, Beck K, Portwood C, Sexton H, Kumarendran M, Brandon Z, *et al.* **Adverse perinatal outcomes associated with protease inhibitor-based antiretroviral therapy in pregnant women living with HIV: A systematic review and meta-analysis.** *EClinicalMedicine* 2022; **46**:101368.
- 19 Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, *et al.* **National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications.** *The Lancet* 2012; **379**:2162–2172.
- 20 Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al.* **National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010.** *Lancet Glob Health* 2013; **1**:e26–e36.
- 21 Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, *et al.* **International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project.** *The Lancet* 2014; **384**:857–868.
- 22 Lawn JE, Cousens S, Zupan J. 4 Million neonatal deaths: When? Where? Why? *Lancet.* 2005; **365**:891–900.
- 23 Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, *et al.* **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.** *Ottawa Hospital Research Institute* 2014; **113**:198–199.
- 24 Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, *et al.* Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* 2009; **6**. doi:10.1371/journal.pmed.1000097
- 25 Ai-jie L, Yong-zhong W. **Study on Low Birth Weight and Correlates of Infants Born by HIV Positive Woman.** *The Chinese Journal of Dermatovenereology* 2013; **27**:161–163.
- 26 Bailey H, Townsend CL, Semenenko I, Malyuta R, Cortina-Borja M, Thorne C. **Impact of expanded access to combination antiretroviral therapy in pregnancy: results from a cohort study in Ukraine.** *Bull World Health Organ* 2013; **91**:491–500.
- 27 Chakornbandit B, Tongprasert F. **Comparison of Preterm Delivery Rates between HIV-infected Pregnant Women Receiving Highly Active Antiretroviral Therapy (HAART) Containing Protease Inhibitors (PIs) and HIV-infected Pregnant Women Receiving Zidovudine Monotherapy.** *Thai Journal of Obstetrics and Gynaecology* 2015; **23**:68–75.
- 28 Chaudhury S, Mayondi GK, Williams PL, Leidner J, Shapiro R, Diseko M, *et al.* **In-utero exposure to antiretrovirals and neurodevelopment among HIV-exposed-uninfected children in Botswana.** *AIDS* 2018; **32**:1173–1183.
- 29 Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogwu A, Lockman S, *et al.* **Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana.** *Journal of Infectious Diseases* 2012; **206**:1695–1705.

- 30 Chetty T, Thorne C, Coutsooudis A. **Preterm delivery and small-for-gestation outcomes in HIV-infected pregnant women on antiretroviral therapy in rural South Africa: Results from a cohort study, 2010-2015.** *PLoS One* 2018; **13**. doi:10.1371/journal.pone.0192805
- 31 Chibwesha CJ, Zanolini A, Smid M, Vwalika B, Phiri Kasaro M, Mwanahamuntu M, *et al.* **Predictors and outcomes of low birth weight in Lusaka, Zambia.** *International Journal of Gynecology and Obstetrics* 2016; **134**:309–314.
- 32 Darak S, Darak T, Kulkarni S, Kulkarni V, Parchure R, Hutter I, *et al.* **Effect of highly active antiretroviral treatment (HAART) during pregnancy on pregnancy outcomes: Experiences from a PMTCT program in Western India.** *AIDS Patient Care STDS* 2013; **27**:163–170.
- 33 Dryden-Peterson S, Jayeoba O, Hughes MD, Jibril H, Keapoletswe K, Tlale J, *et al.* **Highly active antiretroviral therapy versus zidovudine for prevention of mother-to-child transmission in a programmatic setting, Botswana.** *J Acquir Immune Defic Syndr (1988)* 2011; **58**:353–357.
- 34 Grosch-Woerner I, Puch K, Maier RF, Niehues T, Notheis G, Patel D, *et al.* **Increased rate of prematurity associated with antenatal antiretroviral therapy in a German/Austrian cohort of HIV-1-infected women.** *HIV Med* 2008; **9**:6–13.
- 35 Kakkar F, Boucoiran I, Lamarre V, Ducruet T, Amre D, Soudeyns H, *et al.* **Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: Role of ritonavir boosting?** *J Int AIDS Soc* 2015; **18**. doi:10.7448/IAS.18.1.19933
- 36 Kowalska A, Niemiec T, el Midaoui A, Burkacka E. **Effect of antiretroviral therapy on pregnancy outcome in HIV-1 positive women.** *Med Wieku Rozwoj* 2003; **7**:459–468.
- 37 Machado ES, Hofer CB, Costa TT, Nogueira SA, Oliveira RH, Abreu TF, *et al.* **Pregnancy outcome in women infected with hiv-1 receiving combination antiretroviral therapy before versus after conception.** *Sex Transm Infect* 2009; **85**:82–87.
- 38 Martí C, Peña JM, Bates I, Madero R, de José I, Pallardo LF, *et al.* **Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003.** *Acta Obstet Gynecol Scand* 2007; **86**:409–415.
- 39 Moodley T, Moodley D, Sebitloane M, Maharaj N, Sartorius B. **Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa.** *BMC Pregnancy Childbirth* 2016; **16**. doi:10.1186/s12884-016-0821-3
- 40 Njom Nlend AE, Nga Motazé A, Moyo Tetang S, Zeudja C, Ngantcha M, Tejiokem M. **Preterm Birth and Low Birth Weight after In Utero Exposure to Antiretrovirals Initiated during Pregnancy in Yaoundé, Cameroon.** *PLoS One* 2016; **11**:e0150565.
- 41 Powis KM, Smeaton L, Hughes MD, Tumbare EA, Souda S, Jao J, *et al.* **In-utero triple antiretroviral exposure associated with decreased growth among HIV-exposed uninfected infants in Botswana.** *AIDS* 2016; **30**:211–220.
- 42 Ramokolo V, Goga AE, Lombard C, Doherty T, Jackson DJ, Engebretsen IM. **In Utero ART Exposure and Birth and Early Growth Outcomes Among HIV-Exposed Uninfected Infants Attending Immunization Services: Results From National PMTCT Surveillance, South Africa.** *Open Forum Infect Dis* 2017; **4**. doi:10.1093/ofid/ofx187
- 43 Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG. **Declines in low birth weight and preterm birth among infants who were born to HIV-infected women during an era of increased use of maternal antiretroviral drugs: Pediatric spectrum of HIV disease, 1989-2004.** *Pediatrics* 2007; **119**. doi:10.1542/peds.2006-1123

- 44 Sebitloane HM, Moodley J. **Maternal and obstetric complications among HIV-infected women treated with highly active antiretroviral treatment at a Regional Hospital in Durban, South Africa.** *Niger J Clin Pract* 2017; **20**:1360–1367.
- 45 Short CE, Douglas M, Smith JH, Taylor GP. **Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission.** *HIV Med* 2014; **15**:233–238.
- 46 Sibiude J, Warszawski J, Tubiana R, Dollfus C, Faye A, Rouzioux C, *et al.* **Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: Role of the ritonavir boost?** *Clinical Infectious Diseases* 2012; **54**:1348–1360.
- 47 Taylor G, Douglas M, Smith J. **High preterm delivery rates associated with initiation of HAART during pregnancy.** *J Int AIDS Soc* 2010; **13**:P158–P158.
- 48 The Kesho Bora Study Group. **Eighteen-month follow-up of HIV-1-infected mothers and their children enrolled in the Kesho Bora Study observational cohorts.** *J Acquir Immune Defic Syndr (1988)* 2010; **54**:533–541.
- 49 Zash R, Souda S, Chen JY, Binda K, Dryden-Peterson S, Lockman S, *et al.* **Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana.** *Journal of Acquired Immune Deficiency Syndromes* 2016. pp. 428–436.
- 50 **Committee Opinion No 700: Methods for Estimating the Due Date.** *Obstetrics & Gynecology* 2017; **129**:e150–e154.
- 51 WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. Geneva; 2013.
- 52 Uthman OA, Nachega JB, Anderson J, Kanters S, Mills EJ, Renaud F, *et al.* **Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis.** *Lancet HIV* 2017; **4**:e21–e30.
- 53 Stringer JSA, Stoner MC, Kasaro MP, Vwalika B, Cole SR. Preconception ART and preterm birth: real effect or selection bias? *Lancet HIV*. 2017; **4**:e150.
- 54 Sexton H, Kumarendran M, Brandon Z, Shi C, Kirtley S, Hemelaar J. **Adverse perinatal outcomes associated with timing of initiation of antiretroviral therapy: Systematic review and meta-analysis.** *HIV Med*: 2022. doi:10.1111/HIV.13326
- 55 Koss CA, Natureeba P, Plenty A, Luwedde F, Mwesigwa J, Ades V, *et al.* **Risk factors for preterm birth among HIV-infected pregnant ugandan women randomized to lopinavir/ritonavir-or efavirenz-based antiretroviral therapy.** *J Acquir Immune Defic Syndr (1988)* 2014; **67**:128–135.
- 56 Barros FC, Papageorgiou AT, Victora CG, Noble JA, Pang R, Iams J, *et al.* **The distribution of clinical phenotypes of preterm birth syndrome implications for prevention.** *JAMA Pediatr* 2015; **169**:220–229.
- 57 Paiardini M, Müller-Trutwin M. **HIV-associated chronic immune activation.** *Immunol Rev* 2013; **254**:78–101.
- 58 Ravi K, Chan CYS, Akoto C, Zhang W, Vatish M, Norris SA, *et al.* **Changes in the Vα7.2+ CD161++ MAIT cell compartment in early pregnancy are associated with preterm birth in HIV-positive women.** *American Journal of Reproductive Immunology* 2020; **83**. doi:10.1111/aji.13240

- 59 Akoto C, Chan CYS, Tshivuila-Matala COO, Ravi K, Zhang W, Vatish M, *et al.* **Innate lymphoid cells are reduced in pregnant HIV positive women and are associated with preterm birth.** *Sci Rep* 2020; **10**:1–13.
- 60 Akoto C, Norris SA, Hemelaar J. **Maternal HIV infection is associated with distinct systemic cytokine profiles throughout pregnancy in South African women.** *Scientific Reports* 2021 **11**:1 2021; **11**:1–15.
- 61 Papp E, Mohammadi H, Loutfy MR, Yudin MH, Murphy KE, Walmsley SL, *et al.* **HIV Protease Inhibitor Use During Pregnancy Is Associated With Decreased Progesterone Levels, Suggesting a Potential Mechanism Contributing to Fetal Growth Restriction.** *Journal of Infectious Diseases* 2015; **211**:10–18.
- 62 Mohammadi H, Papp E, Cahill L, Rennie M, Banko N, Pinnaduwa L, *et al.* **HIV antiretroviral exposure in pregnancy induces detrimental placenta vascular changes that are rescued by progesterone supplementation.** *Scientific Reports* 2018 **8**:1 2018; **8**:1–14.
- 63 Price JT, Vwalika B, Freeman BL, Cole SR, Saha PT, Mbewe FM, *et al.* **Weekly 17 alpha-hydroxyprogesterone caproate to prevent preterm birth among women living with HIV: a randomised, double-blind, placebo-controlled trial.** *Lancet HIV* 2021; **8**:e605–e613.
- 64 Kintu K, Malaba TR, Nakibuka J, Papamichael C, Colbers A, Byrne K, *et al.* **Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DOLPHIN-2): an open-label, randomised controlled trial.** *Lancet HIV* 2020; **7**:e332–e339.
- 65 Lockman S, Brummel SS, Ziemia L, Stranix-Chibanda L, McCarthy K, Coletti A, *et al.* **Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial.** *The Lancet* 2021; **397**:1276–1292.