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Perinatal outcomes associated with antiretroviral therapy: systematic review and network meta-analysis of randomised controlled trials.

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Abstract

Objective: Assess adverse perinatal outcomes associated with antenatal antiretroviral therapy (ART) regimens.

Design: Systematic review and network meta-analysis of randomised controlled trials (RCTS).

Methods: We conducted a systematic literature review by searching PubMed, CINAHL, Global Health, EMBASE, and the Cochrane Central Register of Controlled Trials and four clinical trial databases from January 1, 1980 to April 28, 2018. We included RCTs of antenatal ART regimens in HIV-positive pregnant women, which assessed preterm birth (PTB), spontaneous preterm birth (sPTB), very preterm birth (VPTB), low birthweight (LBW), very low birthweight (VLBW), small-for-gestational-age (SGA), neonatal death (NND), and mother-to-child-transmission. We used random-effects network meta-analysis models to calculate relative risks for treatment comparisons and the hierarchy of treatments.

Results: Of 83260 citations identified, ten manuscripts were included, assessing 6285 women. Compared to zidovudine (AZT) monotherapy, we found a higher risk of LBW after exposure to zidovudine/lamivudine/efavirenz (AZT/3TC/EFV; relative risk 1.61; 95%CI 1.03-2.51), tenofovir disoproxil fumarate/emtricitabine/ritonavir-boosted lopinavir (TDF/FTC/LPV/r; 1.64; 1.18-2.29), or zidovudine/lamivudine/ritonavir-boosted lopinavir (AZT/3TC/LPV/r; 1.87; 1.58-2.20). TDF/FTC/LPV/r carried an increased risk of VLBW, compared to AZT monotherapy (5.40; 1.08-27.08). AZT/3TC/LPV/r posed a higher risk of PTB than AZT monotherapy (1.43; 1.08-1.91) and a higher risk of sPTB than zidovudine/lamivudine/abacavir (AZT/3TC/ABC)(1.81; 1.21-2.71). LPV/r-containing regimens also carried the highest risks of VPTB, SGA and NND, although the limited data showed no significant differences.

Conclusion:

Of the ART regimens assessed in RCTs in pregnancy, LPV/r-containing regimens were associated with the highest risks of adverse perinatal outcomes.

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

Introduction

The vast majority of the estimated 1.3 million HIV-positive pregnant women who give birth every year reside in sub-Saharan Africa,[1] a region which also has the highest rates of neonatal and child mortality.[2] We previously conducted a systematic review and meta-analysis which showed that maternal HIV infection without antiretroviral therapy (ART) is associated with increased risks of preterm birth (PTB; <37 weeks gestation), low birthweight (LBW; <2500g), small-for-gestational-age (SGA;<10^{th} centile) and stillbirth.[3] PTB is the most important cause of neonatal and child mortality globally.[4] Furthermore, SGA babies account for 21.9% of neonatal deaths in low- and middle-income countries (LMICs).[5] PTB and SGA are both causes of LBW, which is frequently used as a surrogate outcome in LMICs, as gestational age is often unknown.[6] Sustainable Development Goal 3 (SDG3) target 3.2 aims to reduce preventable deaths of newborns and children under 5 years, a goal that will be impossible to achieve without addressing the perinatal outcomes that are at the basis of many of these deaths.[7]

Since 2013, the World Health Organization (WHO) recommends that all HIV-infected pregnant women should receive highly-active antiretroviral therapy (HAART) in order to prevent mother-to-child-transmission (MTCT) of HIV.[8] This led to an increase in the

global proportion of pregnant women with HIV who received ART during pregnancy from 44% in 2010 to 82% in 2018, resulting in a 41% reduction in mother-to-child HIV transmission in the same period.[1] In 2015 WHO adopted a 'treat all' approach which recommends that all HIV-infected individuals, including pregnant women, should initiate lifelong ART as soon as possible after diagnosis, regardless of WHO clinical stage or CD4 cell count.[9]

WHO currently recommends integrase inhibitor dolutegravir (DTG) combined with a backbone of tenofovir disoproxil fumarate and lamivudine (TDF/3TC) as first-line regimen.[10] Non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (EFV) with the same backbone is an alternative first line regimen. Boosted protease inhibitors (PIs), preferably ritonavir-boosted lopinavir (LPV/r) or ritonavir-boosted atazanavir (ATV/r), are designated as second-line regimens. Many aspects are taken into account when recommending ART regimens, such as efficacy in viral suppression, tolerability/adherence, drug resistance, side effects such as weight gain, drug availability and cost.[10, 11] In pregnancy, additional considerations need to be taken into account, such as effectiveness in prevention of vertical transmission of HIV and potential risk of congenital abnormalities, such as neural tube defects (NTD).[10-12] The impact of different ART regimens on other important perinatal outcomes such as PTB, SGA, LBW, stillbirth and neonatal death have been controversial, with conflicting findings reported.[13-16]

With the rapid expansion of ART programs in sub-Saharan Africa it is imperative to determine the optimal ART regimen in pregnancy. We therefore conducted a systematic review and network meta-analysis of randomised controlled trials (RCTs) of ART in HIV-positive pregnant women to assess the association of ART regimens with specific adverse perinatal outcomes.

Methods

Search strategy and selection criteria

We conducted a systematic review and network meta-analysis according to a protocol based on the Cochrane guidelines[17] and registered online (PROSPERO: CRD42013005637). A comprehensive search strategy was developed by a specialist librarian (SK) and co-authors (COOT-M and JH), which was adapted for each database. Both free-text and controlled vocabulary (e.g. MeSH or Emtree) search terms were used, including variations of "HIV" and "ART" and terms indicating specific adverse perinatal outcomes, such as 'preterm birth', or terms indicating general pregnancy outcomes, such as 'pregnancy complication' (Supplementary Methods 1). We searched five electronic literature databases (PUBMED, CINAHL (Ebscohost), Global Health (OVID), EMBASE (OVID), and the Cochrane Central database) and four trial databases (WHO clinical trials database, Pan African Trials database, ClinicalTrials.gov database, and ISRCTN register) to identify studies published between January 1, 1980, and April 28, 2018. No method, country, or language filters were applied; full text articles and abstracts were considered. Retrieved references were imported into Endnote reference manager (Endnote X7; Clarivate Analytics, Philadelphia, PA, USA) and de-duplicated. References of included studies and relevant published reviews were assessed for additional citations.

Three authors (COOTM, SH and CN) independently reviewed the retrieved citations. Selected full text manuscripts were obtained and assessed against the inclusion criteria: population (HIV-positive pregnant women), intervention (antenatal ART regimen), comparison (alternative antenatal ART regimen or placebo), outcomes (see below), and study design (RCTs). All antiretroviral drugs and drug combinations were eligible for inclusion, irrespective of whether they were recommended in current treatment guidelines.

Studies were excluded if an additional intervention was received by only one arm of the trial. Ambiguities about study eligibility were resolved by discussion. If the same trial was reported more than once, manuscripts reporting different perinatal outcomes were included, while ensuring no duplicate data were used in the analysis.[18-23]

Outcomes

Perinatal outcomes, pre-defined in the protocol, included: preterm birth (PTB; $<37^{+0}$ weeks gestation), spontaneous preterm birth (sPTB; $<37^{+0}$ weeks, with spontaneous onset of labor), very preterm birth (VPTB; $<32^{+0}$ weeks), low birthweight (LBW; <2500g), very low birthweight (VLBW; <1500g), small-for-gestational-age (SGA; birthweight for gestational age $<10^{th}$ centile, according to reference chart used locally), and neonatal death (death within first 28 days of life).[3] Mother-to-child transmission was according to the first infant HIV test results reported, representing *in utero* or intrapartum transmission. Data regarding preterm pre-labor rupture of membranes, miscarriage, stillbirth, very small-for-gestational-age, term-low birthweight and preterm-low birthweight were also sought, but no relevant papers were found. Outcome data were not extracted if the outcome was not defined or defined differently from our definitions.

Data extraction and quality assessment

Details about the study, participants, treatment characteristics and perinatal outcomes were extracted by three authors (COOTM, SH and CN) and reviewed by the senior author (JH). Three authors (COOTM, SH and CN) assessed the methodological quality of each RCT using the Cochrane risk of bias tool (Supplementary Methods 2-3) and designated each as having a 'high', 'unclear', or 'low' risk of bias, according to pre-defined criteria (Supplementary Table

1). Any disagreements at each stage of the review process were resolved by consensus or discussion with the senior author (JH).

Data analysis

Perinatal outcome data, stratified according to ART groups, were recorded in 2x2 tables. For each perinatal outcome we plotted network maps of direct treatment comparisons.[24] Each ART regimen was compared to every other ART regimen or placebo in the network through direct, indirect, or combined direct and indirect evidence. Contrast-based multivariate random-effects and, where appropriate, fixed-effects network meta-analysis models were used within a frequentist framework to calculate the weighted summary relative risk (RR) and 95%CI for treatment comparisons, which were displayed in league tables.[24, 25] The augmented data format was used to accommodate multi-arm trials.[26] PROMISE study sub-sets (Periods 1 and 2) were merged using a fixed-effect model in network meta-analyses for PTB, LBW and VLBW. We assumed a common heterogeneity estimate for all treatment comparisons.[25] We estimated the relative ranking probability of each treatment, and obtained the treatment hierarchy of competing ART regimens according to the risk of adverse perinatal outcome using the surface under the cumulative ranking curve (SUCRA).[27] We conducted cluster analyses of the SUCRA estimates in order to group ART regimens with similar profiles together, and represented the results on cluster ranking scatter plots.[28] To meet the transitivity assumption, we applied strict eligibility criteria, which ensured that the methodological, clinical and potential effect modifiers were similar within and across treatment comparisons.[29] The I^2 statistic was used to detect the level of heterogeneity in each meta-analysis.[17] Statistical inconsistency between direct and indirect estimates in each network was assessed using the design-by-treatment interaction model for global inconsistency.[24, 25] Comparison-adjusted funnel plots were used to assess small-study

effects in network meta-analyses.[24, 30] There was no evidence of statistical inconsistency between direct and indirect estimates or publication bias. All statistical analyses were conducted using STATA version 13 (College Station, TX, USA)(Supplementary Methods 4), and the systematic review and network meta-analysis were reported according to the PRISMA guidelines for network meta-analysis.[31]

Results

The electronic literature search yielded 83260 citations; 2101 full text articles and abstracts were retrieved and assessed for eligibility (Figure 1). Ten manuscripts were included, reporting on seven unique RCTs; most were published after 2010 (Table 1).[18-23, 32-36] The included RCTs reported on the association between ART and eight specific adverse perinatal outcomes (Figure 1).

The trials included a total of 6285 HIV-positive pregnant women (Table 1). Four trials were conducted in sub-Saharan Africa and contributed the majority (83.8%) of participants (Table 1). Gestational age was determined using a range of methods, most commonly last normal menstrual period, and all the included trials had a high risk of bias (Table 1, Supplementary Table 1). Most trials enrolled participants with a CD4+ T-lymphocyte count above at least 200cells/µl [20-23, 32-35] and only one trial did not use a CD4+ T-lymphocyte count threshold (Table 2, Supplementary Table 2).[18, 19] Most women were asymptomatic and AIDS-defining illness was rare (Table 2).

Seven different antenatal ART regimens or placebo were initiated during pregnancy to prevent mother-to-child transmission in ART-naïve HIV-positive women. No RCTs assessed the current first-line regimens recommended by WHO, namely TDF/3TC/DTG and TDF/3TC/EFV400. The median gestational age at treatment initiation varied between 21 and 28 weeks (Table 2). Adherence to ART was reported to be high for all studies (Table 2). The

dosages, routes and frequency of administration of each ART drug were identical across all trials, with very few exceptions (Supplementary Table 3).

The network was well-connected and all treatments assessed were connected either directly or indirectly to all other treatments (Figure 2). Most pairwise treatment comparisons were assessed in one trial each, with the exception of the AZT vs AZT/3TC/LPV/r comparison, which was assessed in two trials (Tables 1 & 2, Figure 2).[32, 33]

Six trials including 5471 pregnant women reported on the association between LBW and six ART regimens and placebo (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, zidovudine/lamivudine/efavirenz (AZT/3TC/EFV), tenofovir disoproxil fumarate/emtricitabine/ritonavir-boosted lopinavir (TDF/FTC/LPV/r) and zidovudine/ lamivudine/ritonavir-boosted lopinavir (AZT/3TC/LPV/r) were associated with the highest risks of LBW, and AZT monotherapy exposure had the lowest risk (Table 3A, Supplementary Table 5). In the network meta-analysis, compared to AZT monotherapy, we found a significantly higher risk of LBW after exposure to AZT/3TC/EFV (RR1.61; 95%CI 1.03-2.51), TDF/FTC/LPV/r (1.64; 1.18-2.29) and AZT/3TC/LPV/r (1.87; 1.58-2.20)(Table 3A).

Four trials including 4711 women reported on the association between very LBW (VLBW) and four ART regimens and placebo (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, AZT/3TC/LPV/r, zidovudine/lamivudine/abacavir (AZT/3TC/ABC) and TDF/FTC/LPV/r were associated with the highest risks of VLBW, and AZT monotherapy exposure had the lowest risk (Table 3B, Supplementary Table 5). Exposure to TDF/FTC/LPV/r carried a significantly higher risk of VLBW than exposure to AZT monotherapy (5.40; 1.08-27.08)(Table 3B).

Two trials including 818 women reported on the association between SGA and two ART regimens and placebo (Table 1, Supplementary Figure 1, Supplementary Table 4). In the

SUCRA ranking, AZT/LPV/r had the highest risk of SGA, and AZT monotherapy had the lowest risk (Table 3C, Supplementary Table 5), tough there were no significant differences in the network meta-analysis (Table 3C).

Seven trials including 5789 women reported on the association between PTB and seven ART regimens or placebo (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, TDF/FTC/LPV/r and AZT/3TC/LPV/r were associated with the highest risks of PTB, and exposure to AZT monotherapy and AZT/3TC/ABC had the lowest risks (Table 3D, Supplementary Table 5). Exposure to AZT/3TC/LPV/r carried a significantly higher risk of PTB than exposure to AZT monotherapy (1.43; 1.08-1.91)(Table 3D).

Three trials including 991 women reported on the association between spontaneous PTB (sPTB) and four ART regimens (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, AZT/3TC/LPV/r was associated with the highest risks of sPTB, and exposure to AZT/3TC/ABC had the lowest risk (Table 3E, Supplementary Table 5). Exposure to AZT/3TC/LPV/r carried a significantly higher risk of sPTB than exposure to AZT/3TC/ABC (1.81; 95%CI 1.21-2.71)(Table 3E).

Four trials including 1819 women reported on the association between very PTB (VPTB) and five ART regimens (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, AZT/3TC/LPV/r and LPV/r monotherapy were associated with the highest risks of VPTB, and exposure to AZT monotherapy and AZT/3TC/ABC had the lowest risks (Table 3F, Supplementary Table 5). However, in the network meta-analysis there were no significant differences between the ART regimens assessed (Table 3F).

One trial including 365 women reported on the association between neonatal death and two ART regimens (Table 1, Supplementary Table 4). Direct pairwise analysis showed no significant difference in neonatal deaths for babies exposed antenatally to AZT/3TC/LPV/r compared to AZT/3TC/EFV (1.95; 0.60-6.35)(Supplementary Figure 2).

Seven trials including 5568 women reported on the association between mother-to-child HIV transmission and seven ART regimens or placebo (Table 1, Supplementary Figure 1, Supplementary Table 4). In the SUCRA ranking, LPV/r monotherapy, AZT/3TC/EFV, AZT/3TC/LPV/r, and TDF/FTC/LPV/r, were associated with the lowest risk of mother-to-child transmission. AZT monotherapy and AZT/3TC/ABC were associated with higher risks, and placebo with the highest risk of mother-to-child transmission (Table 3G, Supplementary Table 5). All ART regimens reduced the rate of mother-to-child transmission compared to placebo, some of which met statistical significance: AZT monotherapy (RR 0.30; 95%CI 0.09-0.98), AZT/3TC/LPV/r (0.13; 0.03-0.58), TDF/FTC/LPV/r (0.12; 0.02-0.96), and LPV/r monotherapy (0.02; 0.00-0.88)(Table 3G). There were, however, no significant differences in mother-to-child transmission rates between any of the treatments assessed (Table 3G).

Cluster plots of SUCRA ranking scores of ART regimens for LBW, PTB and mother-to-child transmission showed that AZT/3TC/LPV/r and TDF/FTC/LPV/r had the highest risks of both LBW and PTB, but had relatively high efficacies in prevention of mother-to-child transmission (Supplementary Figure 4 A-B). AZT monotherapy was associated with low risks of both LBW and PTB, but was associated with a relatively high risk of mother-to-child transmission (Supplementary Figure 4 A-B). Interestingly, a correlation between the SUCRA scores for LBW and PTB was evident, with LPV/r-containing HAART regimens being associated with the highest risks of both LBW and PTB, and AZT monotherapy having the lowest risk (Supplementary Figure 4 C).

Discussion

Our analysis shows that the LPV/r-containing HAART regimens AZT/3TC/LPV/r and TDF/FTC/LPV/r are associated with the highest risks of LBW, VLBW, PTB and sPTB. Both regimens are associated with significantly higher LBW rates than AZT monotherapy.

TDF/FTC/LPV/r also has significantly higher VLBW rates than AZT monotherapy. AZT/3TC/LPV/r is associated with both a significantly higher PTB rate than AZT monotherapy and a significantly higher sPTB rate than AZT/3TC/ABC. Although LPV/r-containing regimens also rank lowest (highest risk) for VPTB, SGA and NND, our analyses did not show significant differential effects of ART on these outcomes, though the evidence for these outcomes is limited.

It has not escaped our notice that AZT monotherapy ranked first or second in the SUCRA rankings (i.e. lowest risk) for all outcomes, which included this regimen (LBW, VLBW, SGA, PTB, VPTB) and that the AZT/3TC/ABC regimen carried the lowest risk for all prematurity outcomes (PTB, sPTB and VPTB) in the SUCRA rankings. On the other hand, AZT monotherapy and AZT/3TC/ABC had the lowest rankings (i.e. highest risk) for mother-to-child transmission, after placebo. However, AZT monotherapy carries no long-term benefits for maternal health, prevention of horizontal transmission, or protection of future pregnancies and is, therefore, no longer included in the WHO guidelines.[10] Furthermore, ABC use in LMICs is restricted by the requirement to screen for HLA-B*5701 to avoid the associated hypersensitivity reaction.

This systematic review and network meta-analysis has several important strengths. It is the first study to assess the comparative effects of antenatal ART regimens on a range of specific perinatal outcomes using a network meta-analysis of RCTs. A network meta-analysis has important advantages over traditional pairwise meta-analyses as it enables a synthesis of direct and indirect evidence, allowing all treatments in the network to be compared with one another. Furthermore, it allows ranking of all treatments analyzed for each perinatal outcome.[27] Our study included only RCTs, which have less potential for bias than observational studies. In order to gain a full overview of the available evidence, and in contrast to previous studies, a range of perinatal outcomes were assessed,[16, 37] all classes

of drugs were considered,[37] no restrictions were applied on location where studies were conducted [38] or whether ART regimens were part of current treatment guidelines [39]. In all included RCTs, ART was initiated to prevent mother-to-child transmission in ART-naïve pregnant women, which avoids indication bias. All treatments were initiated antenatally (i.e. not pre-conception) in mostly asymptomatic women with high CD4 cell counts (at least 200cells/μl). The doses, frequencies and routes of administration of individual drugs used in different trials were identical in nearly all instances. All analyses were conducted according to the 'intention-to-treat' principle. The similarities in clinical and treatment characteristics of the included studies meant that the transitivity assumption was met, leading to consistent networks for all outcomes. In addition, we assessed both safety (adverse perinatal outcomes) and efficacy (prevention of mother-to-child transmission) in the same trials, i.e. within the same populations, generating directly comparable data for different outcomes. Most studies were conducted in sub-Saharan Africa, the region with by far the highest burden of maternal HIV infection, thereby enhancing the external validity of our findings. Finally, we worked following a published protocol developed according to Cochrane guidelines; the literature search was comprehensive and at least two independent researchers performed every step. Exposure criteria and outcome definitions were clearly defined *a priori* and strictly applied to minimize selection and misclassification bias. The results were reported according to the PRISMA guidelines for network meta-analysis, thereby minimizing reporting bias.[31]

The main limitation of this study is the relatively limited number of RCTs of antenatal ART regimens that assessed perinatal outcomes. None of the studies included the current WHO preferred first-line regimen TDF/3TC(or FTC)/DTG or the alternative first-line regimen TDF/3TC(or FTC)/EFV400.[10] Perinatal outcomes associated with regimens containing DTG and low dose efavirenz (EFV400) are currently being assessed in RCTs in pregnant women.[40, 41] Unfortunately, each of these new regimens being assessed are distinct from

any of the regimens in the RCTs included in the current network meta-analysis, which will place the new RCT data outside the current network of ART regimens, thereby limiting future comparison to these regimens. Furthermore, few of the included studies examined the same treatment comparison and thereby enabled aggregation (meta-analysis) of direct pairwise data.[32, 33] For the same reasons no meta-regression could be performed as any subgroup or sensitivity analyses would have further limited the networks. Another limitation of the included trials was that they were all classified as having a high risk of bias, principally due to a lack of blinding.

Data from cohort studies on the association between ART regimens and perinatal outcomes have been controversial, with studies reporting conflicting results related to regimen complexity (e.g. AZT monotherapy vs HAART) and type of regimen/class of drugs (e.g. protease inhibitors).[13, 40] For example, in a large cohort study antenatal initiation of HAART was reported to increase the risk of PTB, SGA and SB compared to antenatal initiation of zidovudine monotherapy.[14] However, a subsequent study concluded that antenatal ART initiation was significantly associated with increased risk of very small for gestational age (VSGA) but showed no significant association with PTB and SGA, compared to antenatally initiated zidovudine.[42] Similarly, PI-based HAART was associated with an increased risk of PTB in some studies,[16] but not in others.[43] Women receiving antenatal DTG-based HAART were reported to have similar rates of adverse perinatal outcomes as those on antenatal EFV-based HAART in a cohort study from Botswana.[12, 44]

With the introduction in 2015 of the WHO guidelines recommending initiation of ART in all people living with HIV,[9] a dramatic increase in the proportion of HIV-positive pregnant women conceiving on ART was seen, from 7% in 2010 to 51% in 2018.[1] A recent large retrospective cohort study showed that TDF/FTC/EFV regimen initiated preconception had the lowest risk of adverse and severe adverse birth outcomes, compared with preconception

regimens containing nevirapine (NVP) or LPV/r.[45] However, unadjusted confounding and indication bias of the older and second-line regimens cannot be ruled out. Preconception DTG-based HAART was associated with similar rates of perinatal outcomes, such as PTB and SGA, compared to EFV-based HAART, but was associated with a slightly increased risk of neural tube defects (0.2% excess risk).[12]

A recent systematic review and meta-analysis, which examined observational studies comparing pre-conception with antenatal initiation of ART, concluded that pre-conception initiation was associated with higher rates of PTB, VPTB (defined as <34 weeks' gestation) and LBW.[46] Questions remain regarding unadjusted indication bias between pre-conception and antenatal initiation groups. Moreover, adverse perinatal outcomes in the group of women with planned antenatal initiation might have been missed, as some women delivered prior to ART initiation, as treatment is often commenced very late in pregnancy (selection bias).[47] Crucially, the ART regimens received by the pre-conception and antenatal groups were not identical in individual studies and, given the findings of our network meta-analysis, the associations found may have been due, in part, to the different ART regimens used in the two groups.[46] Thus, the impact of the timing of ART initiation in pregnancy on perinatal outcomes remains uncertain.

The pathogenesis of conditions such as preterm birth, intrauterine growth restriction and stillbirth are extremely complex.[48] In our network meta-analysis, a correlation between the SUCRA scores of ART regimens for LBW and PTB was evident, perhaps because PTB is an important cause of LBW.[6] A number of hypotheses regarding potential mechanisms have been proposed, including inhibition of placental progesterone production by protease inhibitors.[49] Another hypothesis is an immune-mediated mechanism in which ART causes a Th2 to Th1 shift that counteracts the Th1 to Th2 shift seen in pregnancy and ART-naïve HIV infection, although evidence supporting this hypothesis is extremely limited.[50] It is of

paramount importance to better understand these mechanisms in order to devise predictive, preventative and therapeutic interventions to reduce the incidence and impact of these adverse perinatal outcomes.[51] This is particularly urgent in LMICs, which carry the heaviest burden of HIV and adverse perinatal outcomes.

In conclusion, our network meta-analysis of RCTs showed that LPV/r-containing regimens were associated with higher risks of adverse perinatal outcomes compared to the other regimens assessed. Together with data from observational studies [12-15, 42-45] and other meta-analyses [16, 37-39], our findings should help inform treatment guidelines for pregnant HIV-positive women. The rapid expansion of ART programs in sub-Saharan Africa risks further increasing the already high burden of adverse pregnancy outcomes. More research is therefore urgently needed to determine the safest and most efficacious ART regimen in pregnancy to help achieve Sustainable Development Goal 3 in countries with a high HIV prevalence.

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Contributions

COOTM co-wrote the systematic review protocol, assisted with the literature search, screened the search results for relevant manuscripts and assessed their eligibility, conducted

methodological quality assessment, extracted data, co-designed the network meta-analysis plan, conducted the network meta-analysis, interpreted the data and co-wrote the manuscript.

SH and CN screened the literature search results for relevant manuscripts and assessed their eligibility, conducted methodological quality assessment and extracted data.

SK designed and conducted the literature search.

SHK contributed to the coordination of the study and revised the manuscript.

JH conceived, designed and coordinated the study, co-wrote the systematic review protocol, assisted with the literature search, assessment of eligibility of manuscripts, methodological quality assessment, and data extraction, designed the network meta-analysis plan, interpreted the data and wrote the manuscript.

JH had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

All authors read and approved the final version of the manuscript.

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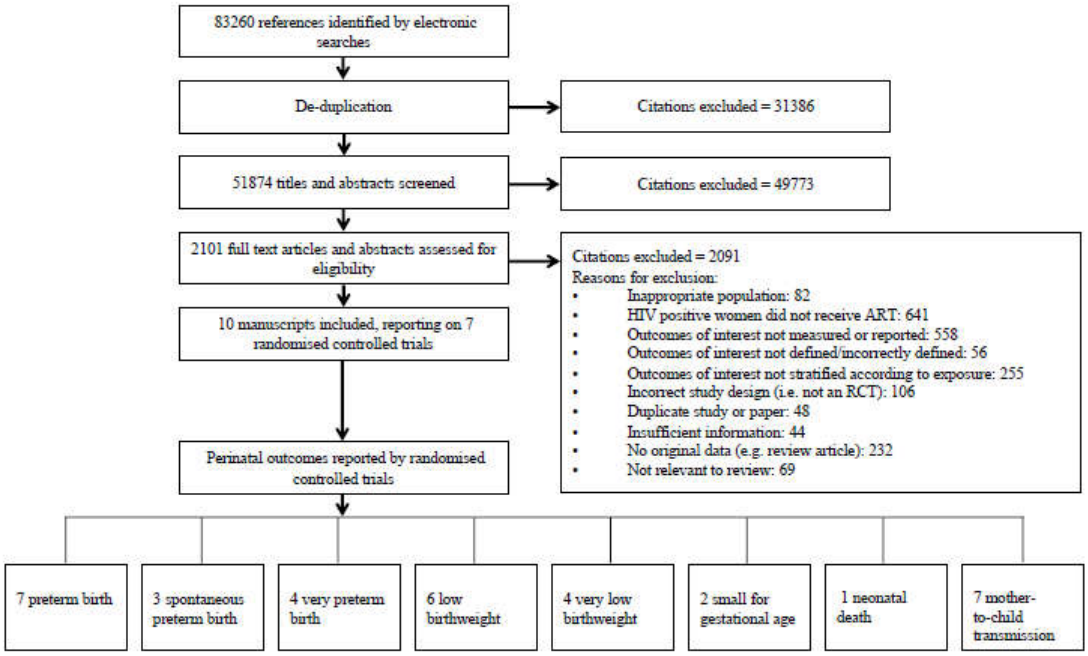

Figure 1. Flow diagram of study selection process.

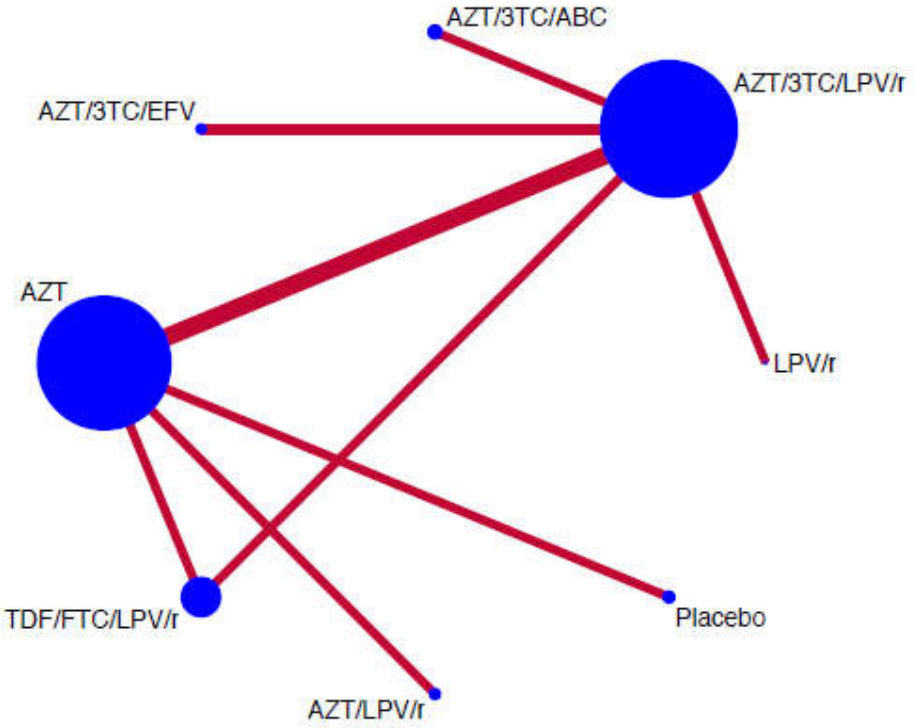

Figure 2. Network plot illustrating direct comparisons between antiretroviral treatments in trials included in the network meta-analysis.

Antiretroviral treatments are represented by circles. The sizes of the circles correspond to the number of participants who received the different antiretroviral treatments. The connecting lines represent head-to-head trial evidence between two antiretroviral treatments. The width of the lines represents the number of trials reporting on the antiretroviral treatment comparisons; each comparison was assessed in one trial, except for the comparison AZT vs AZT/3TC/LPV/r, which was assessed in two trials. Abbreviations: 3TC=lamivudine, ABC=abacavir, AZT=zidovudine, EFV=efavirenz, FTC=emtricitabine, LPV/r=lopinavir/ritonavir, TDF=tenofovir disoproxil fumarate.

Table 1: Study characteristics

Study	Trial	Country	Number of sites	Recruitment time period	Number of pregnant women analysed (n)	Population characteristics [a]	Antenatal treatments	Perinatal outcomes	Risk of bias
Sub-Saharan Africa									
Fowler et al. 2016 [32] (Period 1 & 2)	PROMISE	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	14	April 2011 - 10 September 2014	3088	46.6% from Uganda, Malawi & Tanzania, 33.1% from South Africa, 17.3% from Zimbabwe & Zambia, and 3.0% from India. Women excluded if they had active tuberculosis, tuberculosis treatment within 30 days of trial entry, or hepatitis B virus infection requiring treatment. In the whole study 3.0% had a positive hepatitis B status at enrolment and 1.0% had an infection or infestation. Twin pregnancies included.	1. AZT 2. AZT/3TC/LPV/r	Preterm birth, low birthweight, very low birthweight, mother-to-child transmission	High
Fowler et al. 2016 [32] (Period 2 only)	PROMISE	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	14	October 2012 - 10 September 2014	1230	56.3% from Uganda, Malawi & Tanzania, 16.5% from South Africa, 27.0% from Zimbabwe & Zambia, and 0.2% from India. Women excluded if they had active tuberculosis, TB treatment within 30 days of trial entry, or hepatitis B virus infection requiring treatment. In the whole study 3.0% had a positive hepatitis B status at enrolment and 1.0% had an infection or infestation. Twin pregnancies included.	1. AZT 2. AZT/3TC/LPV/r 3. TDF/FTC/LPV/r	Preterm birth, low birthweight, very low birthweight, mother-to-child transmission	High
Koss et al. 2014 [18]	PROMOTE	Uganda	1	December 2009 - September 2012	356	Women recruited from a district hospital and other health centres in a rural area with high malaria prevalence. 33.4% placental malaria. All women received daily trimethoprim-sulfamethoxazole and were given insecticide-treated bed nets, safe water vessels, multivitamins, and condoms. Women were encouraged to deliver at the hospital. Twin pregnancies excluded.	1. AZT/3TC/LPV/r 2. AZT/3TC/EFV	Preterm birth, spontaneous preterm birth, very preterm birth, mother-to-child transmission [b]	High
Natureeba et al. 2014 [19]	PROMOTE	Uganda	1	December 2009 - March 2013	389	Women recruited from healthcare centres in rural areas with high intensity malaria transmission. 33.3% placental malaria. Women received daily trimethoprim-sulfamethoxazole prophylaxis and were given insecticide-treated bed nets, multivitamins and condoms. 80.4% of deliveries at a healthcare facility, and 19.6% at home. Twin pregnancies included.	1. AZT/3TC/LPV/r 2. AZT/3TC/EFV	Low birthweight, neonatal death, mother-to-child transmission [b]	High
Powis et al. 2011 [23]	Mma Bana Study	Botswana	4	July 2006 - May 2008	530	Urban and rural communities. 3.8% hepatitis B co-infection. 10.6% had at least one sexually transmitted disease before 32 weeks' gestation. No data collected on maternal use of tobacco, alcohol or illicit substances, however, general prevalence reported to be low among Botswana women. Twin pregnancies excluded.	1. AZT/3TC/ABC 2. AZT/3TC/LPV/r	Spontaneous preterm birth	High
Shapiro et al. 2010 [22]	Mma Bana Study	Botswana	4	July 2006 - May 2008	560	Urban and rural communities. 4.3% hepatitis B co-infection. Twin pregnancies included.	1. AZT/3TC/ABC 2. AZT/3TC/LPV/r	Preterm birth, very preterm birth, low birthweight, very low birthweight, mother-to-child transmission	High
The Kesho Bora Study Group 2011 [33]	Kesho Bora Study	Burkina Faso, Kenya, South Africa	5	June 2005 - August 2008	824	Recruitment from antenatal clinics associated with rural and urban study sites. 8.3% had a co-infection, including 2.3% tuberculosis, 1.0% malaria and 1.1% pneumonia. Twin pregnancies included.	1. AZT 2. AZT/3TC/LPV/r	Preterm birth, very preterm birth, low birthweight, very low birthweight, mother-to-child transmission	High
Europe and the Americas									
Connor et al. 1994 [20]	PACTG 076	France, USA	59	11 April 1991 - 20 December 1993	477	Women recruited from healthcare centres. 21.6% had a sexually transmitted disease and 15.9% had a history of injection drug use. Twin pregnancies included.	1. Placebo 2. AZT	Low birthweight, very low birthweight, mother-to-child transmission	High
Sperling et al. 1998 [21]	PACTG 076	France, USA	55	11 April 1991 - 20 December 1993	477	Women recruited from healthcare centres. 44% had a bacterial infection, 42% had a viral infection, and 21% had a fungal infection. Twin pregnancies excluded.	1. Placebo 2. AZT	Preterm birth, small for gestational age	High
Tubiana et al. 2013 [34]	ANRS 135 PRIMEVA	France	19	14 June 2007 - 29 June 2010	105	Women enrolled at sites participating in the French Perinatal Cohort. 72.5% in the monotherapy group and 77.8% in the HAART group were originally from sub-Saharan Africa. 2.9% smoked more than 10 cigarettes per day. Twin pregnancies excluded.	1. LPV/r 2. AZT/3TC/LPV/r	Preterm birth, spontaneous preterm birth, very preterm birth, mother-to-child transmission	High
Asia									
Lallemant et al. 2015 [35]	PHPT-5	Thailand	43	9 January 2009 - 30 September 2010	435	Women participating in the Thai national PMTCT program and intending delivery and postnatal care at one of the study sites. 4.9% infected with hepatitis B and 3.2% with hepatitis C virus. Twin pregnancies included.	1. AZT 2. AZT 3. AZT/LPV/r	Preterm birth, low birthweight, small for gestational age, mother-to-child transmission	High

[a] Data extracted for recruitment, rural/urban setting, co-infections, drug use/smoking status, place of delivery, and twins, if reported. Data from publications reporting on the same trial (Koss et al 1994[18]/Natureeba et al 1994[19]; Shapiro et al 2010[22]/Powis et al 2011[23]; Conner et al 1994[20]/Sperling et al 1998[21]) is given as reported in each publication, but will be broadly applicable to the other publication reporting on the same trial.

[b] Data on mother-to-child transmission extracted from Cohan et al. 2015.[16]

Abbreviations: 3TC = lamivudine, ABC = abacavir, AZT = zidovudine, EFV = efavirenz, FTC = emtricitabine, HAART = Highly Active Antiretroviral Treatment, LPV/r = lopinavir/ritonavir, PACTG 076 = Pediatric AIDS Clinical Trials Group Protocol 076 Study Group, PHPT-5 = Perinatal HIV Prevention Trial-5, PMTCT = prevention of mother to child transmission, PRIMEVA = Protease Inhibitor Monotherapy Evaluation study, PROMISE = Promoting Maternal and Infant Survival Everywhere, PROMOTE = Pregnant Women and Infants Study, USA = United States of America

Table 2: Participant and antiretroviral treatment characteristics

Study (Trial)	Antenatal treatments	Number of pregnant women analysed (n)	Participant characteristics					Antiretroviral treatment characteristics		
			Maternal age (years) [mean±SD / median (IQR)]	Race	Caesarean section rate (%)	CD4+ T-lymphocyte count threshold for trial enrolment (cells/μL)	HIV stage of disease	Antenatal treatment initiation (weeks gestation) [median (IQR) / mean ± SD]	Duration of antenatal treatment (weeks) [median (IQR)]	Adherence (%)
Sub-Saharan Africa										
Fowler et al. 2016 [32] (Period 1 & 2) (PROMISE)	1. AZT	1545	26 (22 - 30)	Black African = 96.9% Native Indian = 3.0% Other = 0.1%	-	≥ 350 or country-specific threshold if that threshold was higher	WHO 1 = 96.5% WHO 2 = 3.4% WHO 3 = 0.1%	26 (21 - 30)	Until delivery (Unspecified)	Entire study: 4% discontinued assigned ART prematurely.
	2. AZT/3TC/LPV/r	1543	26 (23 - 30)	Black African = 97.0% Native Indian = 3.0% Other = 0.1%	-	≥ 350 or country-specific threshold if that threshold was higher	WHO 1 = 97.7% WHO 2 = 2.2% WHO 3 = 0.1%	25 (21 - 30)	Until delivery (Unspecified)	Entire study: 4% discontinued assigned ART prematurely.
Fowler et al. 2016 [32] (Period 2 only) (PROMISE)	1. AZT	413	25 (22 - 29)	Black African = 100%	-	≥ 350 or country-specific threshold if that threshold was higher	WHO 1 = 96.6% WHO 2 = 3.4%	26 (21 - 31)	Until delivery (Unspecified)	Entire study: 4% discontinued assigned ART prematurely.
	2. AZT/3TC/LPV/r	410	26 (23 - 30)	Black African = 100%	-	≥ 350 or country-specific threshold if that threshold was higher	WHO 1 = 97.3% WHO 2 = 2.7%	26 (21 - 31)	Until delivery (Unspecified)	Entire study: 4% discontinued assigned ART prematurely.
	3. TDF/FTC/LPV/r	407	26 (22 - 30)	Black African = 100%	-	≥ 350 or country-specific threshold if that threshold was higher	WHO 1 = 98.3% WHO 2 = 1.7%	26 (22 - 31)	Until delivery (Unspecified)	Entire study: 4% discontinued assigned ART prematurely.
Koss et al. 2014 [18] (PROMOTE)	1. AZT/3TC/LPV/r	179	29 (25 - 33)	-	Entire study: 5.3%	Any CD4+ T-lymphocyte count	Entire study: WHO 1 = 96%	21 (17 - 25)	Until delivery (Unspecified)	-
	2. AZT/3TC/EFV	177	30 (26 - 33)	-	Entire study: 5.3%	Any CD4+ T-lymphocyte count	Entire study: WHO 1 = 96%	21 (18 - 24)	Until delivery (Unspecified)	-
Natureeba et al. 2014 [19] (PROMOTE)	1. AZT/3TC/LPV/r	194	29.0 ± 5.4	-	-	Any CD4+ T-lymphocyte count	WHO 1 = 97.4% WHO 2 = 2.6%	21.2 ± 4.3	Until delivery (Unspecified)	99%
	2. AZT/3TC/EFV	195	29.5 ± 5.4	-	-	Any CD4+ T-lymphocyte count	WHO 1 = 92.8% WHO 2 = 6.7% WHO 3 = 0.5%	21.1 ± 4.1	Until delivery (Unspecified)	97%
Powis et al. 2011 [23] (Mma Bana Study)	1. AZT/3TC/ABC	263	26.8 (23.0 -31.6)	-	0%	≥ 200	Entire study: No AIDS defining disease	Distribution: 26 - 28= 67.3% 29 - 31= 16.7% 32 - 34= 16.0%	11.6 (8.3 - 13.3)	Entire study: 99.6% still receiving originally assigned ART at delivery.
	2. AZT/3TC/LPV/r	267	26.0 (23.0 -30.4)	-	0%	≥ 200	Entire study: No AIDS defining disease	Distribution: 26 - 28= 67.4% 29 - 31= 23.6% 32 - 34 = 9.0%	11.0 (8.1 - 12.7)	Entire study: 99.6% still receiving originally assigned ART at delivery.
Shapiro et al. 2010 [22] (Mma Bana Study)	1. AZT/3TC/ABC	285	26 *	-	-	≥ 200	Entire study: No AIDS defining disease	27.1 (26.4 - 29.9)	11 *	22% missed 1 day or more of ART during pregnancy or breastfeeding.
	2. AZT/3TC/LPV/r	275	25 *	-	-	≥ 200	Entire study: No AIDS defining disease	27.1 (26.4 - 29.9)	11 *	22% missed 1 day or more of ART during pregnancy or breastfeeding.

The Kesho Bora Study Group 2011 [33] (Kesho Bora Study)	1. AZT	412	27 (23 - 31)	-	12.5%	200 - 500	Entire study: WHO stage 1, 2 or 3	Entire study: Range: 28 - 36	6.4 (4.3 - 8.8)	73% missed no doses before delivery.
	2. AZT/3TC/LPV/r	412	27 (24 - 31)	-	10.9%	200 - 500	Entire study: WHO stage 1, 2 or 3	Entire study: Range: 28 - 36	6.0 (4.1 - 8.4)	73% missed no doses before delivery.
Europe and the Americas										
Connor et al. 1994 [20] (PACTG 076)	1. Placebo	238	25 [a]	Caucasian = 16.6%, Black = 55.4%, Hispanic = 26.6%, Other = 1.3%	25.2%	>200	-	Entire study: Range:14 - 34	Entire study: 11 (0 - 26) [b]	6.3% incomplete treatment
	2. AZT	239	25 [a]	Caucasian = 20.7% Black = 46.1% Hispanic = 30.6% Other = 2.6%	29.4%	>200	-	Entire study: Range:14 - 34	Entire study: 11 (0 - 26) [b]	3.8% incomplete treatment
Sperling et al. 1998 [21] (PACTG 076)	1. Placebo	238	-	-	23.6%	>200	CDC-B = 21% CDC-C = 2%	-	Until delivery (Unspecified)	7% premature treatment discontinuation
	2. AZT	239	-	-	27.7%	>200	CDC-B = 21% CDC-C = 2%	-	Until delivery (Unspecified)	5% premature treatment discontinuation
Tubiana et al. 2013 [34] (ANRS 135 PRIMEVA)	1. LPV/r	69	30 (18 - 44) [b]	-	50.7%	≥350	-	26.0 (24 - 27) [b]	90 (50 - 111) days [b]	Entire study: At 8 weeks of treatment 75.4% did not miss a pill in the previous 4 days or weeks
	2. AZT/3TC/LPV/r	36	29 (18 - 42) [b]	-	47.2%	≥350	-	26.0 (25 - 27) [b]	90 (57 - 111) days [b]	Entire study: At 8 weeks of treatment 75.4% did not miss a pill in the previous 4 days or weeks
Asia										
Lallemant et al. 2015 [35] (PHPT-5)	1. AZT	139	28 (23.0 -33.0)	-	31.3%	Before 4 June 2010: ≥ 250, after 4 June 2010: ≥ 350	WHO 1 = 98.4% WHO 2 = 1.6%	28.3 (28.0 - 28.9)	10.3 (9.1 - 11.4)	Adherence more than 90% for zidovudine = 96.8% (entire study cohort)
	2. AZT	144	27 (23.0 -32.0)	-	28.9%	Before 4 June 2010: ≥ 250, after 4 June 2010: ≥ 350	WHO 1 = 97.1% WHO 2 = 2.9%	28.4 (28.0 - 29.0)	10.1 (8.1 - 11.1)	Adherence more than 90% for zidovudine = 96.8% (entire study cohort)
	3. AZT/LPV/r	152	27 (23.0 -32.0)	-	31.7%	Before 4 June 2010: ≥ 250, after 4 June 2010: ≥ 350	WHO 1 = 97.9% WHO 2 = 2.1%	28.3 (28.0 - 29.0)	10.0 (8.6 - 11.1)	Adherence more than 90% for zidovudine = 96.8% (entire study cohort) Adherence more than 90% for lopinavir/ ritonavir = 95.2%

[a] Median, [b] Median (range).

Abbreviations: 3TC = lamivudine, ABC = abacavir, AIDS = Aquired Immuno-Deficiency Syndrome, ART = antiretroviral treatment, AZT = zidovudine, CDC = Centers for Disease Control and Prevention, CI = Confidence Interval, EFV = efavirenz, FTC = emtricitabine, HIV = Human Immunodeficiency Virus, IQR = inter quartile range, LPV/r = lopinavir/ritonavir, PACTG 076 = Pediatric AIDS Clinical Trials Group Protocol 076 Study Group, PHPT-5 = Perinatal HIV Prevention Trial-5, PRIMEVA = Protease Inhibitor Monotherapy Evaluation study, PROMISE = Promoting Maternal and Infant Survival Everywhere, PROMOTE = Pregnant Women and Infants Study, SD = standard deviation, TDF = tenofovir disoproxil fumarate, WHO = World Health Organization.

Table 3. League tables of network meta-analysis results for the association between antenatal antiretroviral treatments and perinatal outcomes.

A. Low birthweight

AZT	1.13 (0.69 - 1.87)	1.30 (0.83 - 2.05)	1.46 (0.95 - 2.26)	1.61 (1.03 - 2.51)	1.64 (1.18 - 2.29)	1.87 (1.58 - 2.20)
0.88 (0.54 - 1.46)	AZT/LPV/r	1.15 (0.59 - 2.26)	1.29 (0.67 - 2.51)	1.42 (0.73 - 2.78)	1.45 (0.80 - 2.65)	1.65 (0.97 - 2.79)
0.77 (0.49 - 1.21)	0.87 (0.44 - 1.70)	Placebo	1.12 (0.60 - 2.10)	1.23 (0.65 - 2.33)	1.26 (0.72 - 2.21)	1.43 (0.89 - 2.32)
0.68 (0.44 - 1.05)	0.77 (0.40 - 1.50)	0.89 (0.48 - 1.66)	AZT/3TC/ABC	1.10 (0.62 - 1.95)	1.12 (0.67 - 1.87)	1.27 (0.85 - 1.91)
0.62 (0.40 - 0.97)	0.70 (0.36 - 1.38)	0.81 (0.43 - 1.53)	0.91 (0.51 - 1.62)	AZT/3TC/EFV	1.02 (0.61 - 1.72)	1.16 (0.77 - 1.76)
0.61 (0.44 - 0.85)	0.69 (0.38 - 1.26)	0.79 (0.45 - 1.39)	0.89 (0.54 - 1.49)	0.98 (0.58 - 1.65)	TDF/FTC/LPV/r	1.14 (0.83 - 1.56)
0.54 (0.46 - 0.63)	0.61 (0.36 - 1.03)	0.70 (0.43 - 1.13)	0.78 (0.52 - 1.17)	0.86 (0.57 - 1.30)	0.88 (0.64 - 1.20)	AZT/3TC/LPV/r

B. Very low birthweight

AZT	1.31 (0.30 - 5.85)	1.57 (0.31 - 7.87)	6.00 (0.40 - 90.96)	5.40 (1.08 - 27.08)
0.76 (0.17 - 3.39)	Placebo	1.20 (0.13 - 10.75)	4.56 (0.21 - 101.52)	4.11 (0.46 - 36.99)
0.64 (0.13 - 3.19)	0.84 (0.09 - 7.52)	AZT/3TC/LPV/r	3.82 (0.43 - 34.13)	3.43 (0.69 - 17.10)
0.17 (0.01 - 2.53)	0.22 (0.01 - 4.87)	0.26 (0.03 - 2.34)	AZT/3TC/ABC	0.90 (0.06 - 13.60)
0.19 (0.04 - 0.93)	0.24 (0.03 - 2.19)	0.29 (0.06 - 1.45)	1.11 (0.07 - 16.81)	TDF/FTC/LPV/r

C. Small for gestational age

AZT	1.11 (0.69 - 1.79)	1.57 (0.70 - 3.54)
0.90 (0.56 - 1.44)	Placebo	1.41 (0.55 - 3.62)
0.64 (0.28 - 1.44)	0.71 (0.28 - 1.82)	AZT/LPV/r

D. Preterm birth

AZT/3TC/ABC	1.06 (0.63 - 1.79)	1.07 (0.54 - 2.10)	1.27 (0.59 - 2.74)	1.39 (0.39 - 4.92)	1.38 (0.69 - 2.77)	1.45 (0.82 - 2.59)	1.52 (0.99 - 2.35)
0.94 (0.56 - 1.59)	AZT	1.00 (0.65 - 1.55)	1.20 (0.68 - 2.11)	1.31 (0.39 - 4.44)	1.30 (0.70 - 2.41)	1.37 (0.93 - 2.01)	1.43 (1.08 - 1.91)
0.94 (0.48 - 1.85)	1.00 (0.64 - 1.54)	Placebo	1.19 (0.59 - 2.43)	1.30 (0.36 - 4.76)	1.29 (0.61 - 2.75)	1.36 (0.76 - 2.43)	1.43 (0.85 - 2.40)
0.79 (0.36 - 1.69)	0.83 (0.47 - 1.47)	0.84 (0.41 - 1.71)	AZT/LPV/r	1.09 (0.28 - 4.19)	1.08 (0.47 - 2.50)	1.14 (0.58 - 2.26)	1.20 (0.63 - 2.25)
0.72 (0.20 - 2.55)	0.76 (0.23 - 2.59)	0.77 (0.21 - 2.80)	0.92 (0.24 - 3.52)	LPV/r	0.99 (0.27 - 3.67)	1.04 (0.30 - 3.63)	1.10 (0.33 - 3.59)
0.72 (0.36 - 1.46)	0.77 (0.41 - 1.43)	0.77 (0.36 - 1.64)	0.92 (0.40 - 2.13)	1.01 (0.27 - 3.72)	AZT/3TC/EFV	1.05 (0.54 - 2.05)	1.10 (0.64 - 1.90)
0.69 (0.39 - 1.23)	0.73 (0.50 - 1.07)	0.73 (0.41 - 1.31)	0.88 (0.44 - 1.73)	0.96 (0.28 - 3.33)	0.95 (0.49 - 1.85)	TDF/FTC/LPV/r	1.05 (0.72 - 1.53)
0.66 (0.43 - 1.01)	0.70 (0.52 - 0.93)	0.70 (0.42 - 1.18)	0.84 (0.44 - 1.58)	0.91 (0.28 - 2.99)	0.91 (0.52 - 1.57)	0.95 (0.65 - 1.40)	AZT/3TC/LPV/r

E. Spontaneous preterm birth

AZT/3TC/ABC	0.95 (0.06 - 15.91)	1.56 (0.81 - 3.00)	1.81 (1.21 - 2.71)
1.06 (0.06 - 17.80)	LPV/r	1.65 (0.10 - 28.28)	1.92 (0.12 - 31.30)
0.64 (0.33 - 1.23)	0.61 (0.04 - 10.38)	AZT/3TC/EFV	1.16 (0.69 - 1.94)
0.55 (0.37 - 0.83)	0.52 (0.03 - 8.53)	0.86 (0.51 - 1.44)	AZT/3TC/LPV/r

F. Very preterm birth

AZT/3TC/ABC	1.04 (0.07 - 15.10)	2.12 (0.29 - 15.39)	2.10 (0.64 - 6.88)	3.32 (0.11 - 100.31)
0.96 (0.07 - 13.95)	AZT	2.04 (0.12 - 36.09)	2.01 (0.18 - 22.13)	3.19 (0.06 - 172.95)
0.47 (0.06 - 3.43)	0.49 (0.03 - 8.69)	AZT/3TC/EFV	0.99 (0.20 - 4.83)	1.57 (0.04 - 55.41)
0.48 (0.15 - 1.57)	0.50 (0.05 - 5.45)	1.01 (0.21 - 4.94)	AZT/3TC/LPV/r	1.59 (0.07 - 38.55)
0.30 (0.01 - 9.08)	0.31 (0.01 - 16.94)	0.64 (0.02 - 22.54)	0.63 (0.03 - 15.34)	LPV/r

G. Mother-to-child transmission

LPV/r	1.97 (0.02 - 215.21)	5.66 (0.21 - 155.00)	5.24 (0.12 - 221.28)	6.97 (0.14 - 339.31)	13.04 (0.42 - 404.58)	21.61 (0.37 - 1271.26)	42.80 (1.14 - 1610.29)
0.51 (0.00 - 55.48)	AZT/3TC/EFV	2.88 (0.10 - 80.20)	2.66 (0.06 - 114.26)	3.54 (0.07 - 175.11)	6.62 (0.21 - 209.23)	10.97 (0.18 - 655.49)	21.73 (0.57 - 832.06)
0.18 (0.01 - 4.83)	0.35 (0.01 - 9.70)	AZT/3TC/LPV /r	0.93 (0.16 - 5.32)	1.23 (0.16 - 9.43)	2.30 (0.92 - 5.77)	3.82 (0.35 - 41.11)	7.56 (1.71 - 33.41)
0.19 (0.00 - 8.05)	0.38 (0.01 - 16.13)	1.08 (0.19 - 6.20)	TDF/FTC/LPV /r	1.33 (0.11 - 15.94)	2.49 (0.46 - 13.54)	4.12 (0.22 - 78.78)	8.16 (1.04 - 63.92)
0.14 (0.00 - 6.99)	0.28 (0.01 - 13.99)	0.81 (0.11 - 6.23)	0.75 (0.06 - 9.03)	AZT/LPV/r	1.87 (0.30 - 11.52)	3.10 (0.14 - 70.94)	6.14 (0.71 - 53.29)
0.08 (0.00 - 2.38)	0.15 (0.00 - 4.77)	0.43 (0.17 - 1.09)	0.40 (0.07 - 2.19)	0.53 (0.09 - 3.29)	AZT	1.66 (0.13 - 21.18)	3.28 (1.02 - 10.55)
0.05 (0.00 - 2.72)	0.09 (0.00 - 5.45)	0.26 (0.02 - 2.82)	0.24 (0.01 - 4.64)	0.32 (0.01 - 7.37)	0.60 (0.05 - 7.72)	AZT/3TC/ABC	1.98 (0.12 - 32.68)
0.02 (0.00 - 0.88)	0.05 (0.00 - 1.76)	0.13 (0.03 - 0.58)	0.12 (0.02 - 0.96)	0.16 (0.02 - 1.41)	0.30 (0.09 - 0.98)	0.50 (0.03 - 8.33)	Placebo

Table 3. League tables of network meta-analysis results for the association between antenatal antiretroviral treatments and perinatal outcomes.

The antiretroviral treatments are ordered from top left to bottom right in the order of descendingSUCRA scores, i.e. the antiretroviral treatment with the highest SUCRA score (lowest risk ofadverse perinatal outcome) is in the top left and the treatment with the lowest SUCRA score(highest risk) is in the bottom right. The tables show all possible pairwise comparisonsgenerated by the network meta-analysis. Results are reported as a relative risk (95%CI) of thecolumn antiretroviral treatment relative to the row antiretroviral treatment (e.g. Figure 3A: topright: AZT/3TC/LPV/r (column) vs AZT (row): the risk of low birthweight associated withAZT/3TC/LPV/r relative to AZT is 1.87 (1.58-2.20)). Statistically significant effects arepresented in red.

Perinatal outcomes: low birthweight (A), very low birthweight (B), small-forgestational-age (C), preterm birth (D), spontaneous preterm birth (E), very preterm birth (F),and mother-to-child transmission of HIV (G).

Abbreviations: 3TC=lamivudine,ABC=abacavir, AZT=zidovudine, EFV=efavirenz, FTC=emtricitabine, LPV/r=lopinavir/ritonavir, TDF=tenofovir disoproxil fumarate.