Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis

Olalekan A Uthman, Jean B Nachega, Jean Anderson, Steve Kanters, Edward J Mills, Françoise Renaud, Shaffiq Essajee, Meg C Doherty, Lynne M Mofenson

Summary

Background Although lifelong combination antiretroviral therapy (ART) is recommended for all individuals with HIV, few data exist for pregnancy outcomes associated with ART initiation before conception. We assessed adverse pregnancy outcomes associated with ART initiated before conception compared with that of ART started after conception.

Methods We did a systematic review of studies from low-income, middle-income, and high-income countries by searching the Cochrane Central Register of Controlled Trials, Embase, LILACS, MEDLINE, Toxline, Web of Knowledge, and WHO Global Index Medicus and trials in progress (International Clinical Trials Registry Platform) for randomised trials, quasi-randomised trials, and prospective cohort studies done between Jan 1, 1980, and June 1, 2016, in which timing of ART initiation in pregnant women living with HIV was reported. We used the risk ratio (RR) and corresponding 95% CIs as the primary measure to assess the association between the selected outcomes and ART initiation before conception versus after conception. We used a random-effects model to pool risk ratios.

Findings We included 11 studies with 19 189 mother–infant pairs. Women who started ART before conception were significantly more likely to deliver preterm (pooled RR 1·20, 95% CI 1·01–1·44) or very preterm (1·53, 1·22–1·92), or to have low-birthweight infants (1·30, 1·04–1·62) than were those who began ART after conception. Few data exist for neonatal mortality. The risk of very low birthweight, small for gestational age, severe small for gestational age, stillbirth, and congenital anomalies did not differ significantly between women who were taking ART before conception and those who began ART after conception.

Interpretation The benefits of ART for maternal health and prevention of perinatal transmission outweigh risks, but data for the extent and severity of these risks are scarce and of low quality. As use of ART before conception rapidly increases globally, monitoring for potential adverse pregnancy outcomes will be crucial.

Funding WHO.

Lancet HIV 2017; 4: e21–30

Published Online November 15, 2016 http://dx.doi.org/10.1016/S2352-3018(16)30195-3

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Introduction

In 2013, WHO recommended that all pregnant and breastfeeding women with HIV infection should initiate combination antiretroviral therapy (ART) irrespective of clinical or immune status, and that ART be continued at least for the duration of mother-to-child transmission risk, with the option of continuing lifelong ART—an approach adopted by many low-income countries as a result of its programmatic and clinical benefits.[1] After the results of the TEMPRANO[2] and START[3] trials showed that beginning ART at higher CD4 cell counts (>500 cells per μL) was associated with significant clinical benefits, in 2015, WHO recommended immediate initiation of lifelong ART for all HIV-infected individuals, including pregnant women.[4] Thus, an increasing proportion of HIV-infected women will become pregnant while receiving ART.

ART started before conception and continued throughout pregnancy is associated with extremely low rates of mother-to-child transmission of HIV. In a report[5] from the UK and Ireland on 5652 deliveries between 2007 and 2011, only four (0·19%) of 2105 women on ART before conception transmitted HIV to their infant. In the French Perinatal Cohort,[6] no cases of mother-to-child transmission were noted among 2651 women who started ART before conception and had achieved viral suppression at delivery.

Lifelong ART for all HIV-infected pregnant women will not only contribute substantially to the global elimination of new paediatric HIV infections and improve maternal health and survival, but will also lead to a rapid rise in fetal exposure to antiretrovirals as pregnant and breastfeeding women started on ART have subsequent pregnancies. Despite nearly two decades of ART use during pregnancy, evidence for safety is scarce and conflicting.[7] ART use during pregnancy has been associated with increased risk of adverse birth outcomes, such as preterm delivery and low birthweight, in reports

Research in context

Evidence before this study

We did a systematic literature review of the Cochrane Central Register of Controlled Trials, Embase, LILACS, MEDLINE, Toxline, Web of Knowledge, and WHO Global Index Medicus and trials in progress (International Clinical Trials Registry Platform) to identify studies published between Jan 1, 1980, and June 1, 2016, in which pregnancy outcomes in pregnant women with HIV initiating antiretroviral therapy (ART) before conception were compared with those in women beginning ART after conception. We found 11 studies including 19 189 women with HIV, 10 232 of whom started ART before conception and 8957 of whom started ART after conception. ART use during pregnancy has been associated with increased risk of adverse birth outcomes, such as preterm delivery and low birthweight, when compared with use of less complex regimens such as zidovudine prophylaxis in some studies in both low-income and high-income countries. The results of some studies have suggested that adverse pregnancy outcomes could be specifically associated with protease inhibitor use during pregnancy, but data from large studies in Botswana and Tanzania suggest such outcomes could also be linked to nevirapine-based or efavirenz-based ART. Very few data are available to allow comparison of pregnancy outcomes in women initiating ART before conception with outcomes in those beginning ART after conception. Until 2013, in low-income settings, where the largest proportion of women living with HIV are, WHO guidelines recommended use of lifelong ART during pregnancy only for pregnant women with low CD4 cell counts or advanced disease. Thus, the number of women who conceived while taking ART was low. In high-income settings, ART was recommended for all pregnant women, but until 2015, many women with high CD4 cell counts (>500 cells per μL) stopped ART after delivery. In some studies, use of ART before conception was compared with use of any regimen during pregnancy, including zidovudine alone, whereas in other studies ART use before conception was combined with first trimester use, without accounting for timing of first trimester initiation.

Added value of this study

To our knowledge, ours is the first systematic review that has specifically assessed adverse pregnancy outcome risks by timing of initiation of ART (ie, before conception *vs* after conception). Although, reassuringly, many adverse outcomes, such as stillbirth, small for gestational age, and congenital abnormalities did not seem to differ by timing of ART initiation, we found that preterm delivery and low birthweight were significantly more likely in women who began ART before conception than in those who began ART after conception. However, data are sparse and of low to very low quality, and correlation with infant mortality or morbidity was not shown.

Implications of all available evidence

Although the clear benefits of ART for maternal health and prevention of perinatal transmission outweigh potential risks, data for the extent or severity of these risks remain few and of poor quality. We showed an increased risk of preterm delivery and low birthweight associated with pre-conception initiation of ART, but there are potential confounders, because ART was used before conception primarily by women with low CD4 cell counts who were felt to require treatment for their health. In view of new guidelines for immediate ART in all individuals with HIV, use of ART before conception can be expected to increase rapidly worldwide, and will be crucial to monitor for potential adverse pregnancy outcomes.

For the **international prospective register of systematic reviews** see http://www.crd.york.ac.uk/PROSPERO

from both high-income and low-income countries.[8–11] Some data suggest that adverse pregnancy outcomes could be specifically associated with use of protease inhibitors during pregnancy;[12–15] other data, including the results of a large population-based study in Botswana[9] and a study in Tanzania,[16] suggest that such outcomes might also be associated with nevirapine-based or efavirenz-based ART. We did a systematic review to summarise the data about safety of, and adverse pregnancy outcomes associated with, ART initiated before conception compared with those of ART started after conception to inform the upcoming WHO 2015 consolidated ART guidelines. We did not address potential longer-term effects of in-utero ART exposure in HIV-exposed but uninfected children.

Methods

Inclusion criteria

We specified in advance the study background, rationale, and methods and documented them in a protocol to be published at the international prospective register of systematic reviews (PROSPERO number CRD42015025189). To be eligible for inclusion in our review, studies had to contain information about pregnancy outcomes after exposure to ART. The selection criteria we used to identify potential studies were study design (randomised trials, quasi-randomised trials, and prospective cohort studies), study population (pregnant women living with HIV and receiving ART), intervention (ART initiation before conception), comparator (ART initiation after conception [first initiated during pregnancy]), and outcomes (prematurity, defined as livebirth at <37 weeks' gestation; very preterm delivery, defined as livebirth at <34 weeks' gestation; low birthweight [<2500 g]; very low birthweight [<1500 g]; small for gestational age, defined as birthweight <10th centile for gestational age; severe small for gestational age, defined as birthweight <3rd centile for gestational age; stillbirth, defined as infant born with no signs of life ≥28 weeks' gestation; maternal mortality;

neonatal mortality; and congenital anomalies, as defined by the authors of the studies).

Data sources and searches

We systematically searched the Cochrane Central Register of Controlled Trials, Embase, LILACS, MEDLINE, Toxline, Web of Knowledge, and WHO Global Index Medicus and trials in progress (International Clinical Trials Registry Platform) for work published in any language between Jan 1, 1980, and June 30, 2016. Our search strategy is provided in the appendix; we used it to search MEDLINE and Embase via OVID, and adapted it to the other search engines. We also reviewed conference abstracts identified by our Embase search and from the International AIDS Conference, the annual Conference on Retroviruses and Opportunistic Infections, and the Conference on HIV Pathogenesis, Treatment, and Prevention (IAS) to find more recent relevant studies (our search of conference abstracts was restricted to those published between Jan 1, 2013, and June 30, 2016).

Additionally, hand searches of bibliographies of published systematic reviews and health technology assessments were done. We also manually searched ClinicalTrials.gov and the metaRegister of Controlled Trials to identify randomised controlled trials that had not yet been published but were potentially eligible for inclusion.

Study selection and data extraction

Two investigators (OAU and JBN), working independently, scanned all abstracts and proceedings identified in the search of published work and reviewed full-text versions of potentially relevant abstracts and proceedings. The same investigators then independently extracted data for study characteristics, interventions, patient characteristics at baseline, and outcomes (unadjusted and adjusted associations) for the study populations of interest for the final list of selected eligible studies. Any discrepancies between investigators were resolved through discussion until consensus was reached. We assessed the quality of evidence for the primary outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[17] For studies in which adjusted outcomes were not reported, we did not contact the authors for missing data, because doing so is usually time-intensive and the additional data requested are rarely acquired in our experience.

Statistical analysis

We used the risk ratio (RR) and corresponding 95% CIs as the primary measure to assess the association between the selected outcomes and ART initiation before conception versus after conception. We used a random-effects model to combine data. The presence of statistical heterogeneity in the meta-analyses was assessed by reviewing the forest plot and applying a χ^2 test for heterogeneity with a threshold p value of 0·10 to determine significance. We used the I^2 value to quantify inconsistency across studies.[18] For preterm delivery, we used funnels plots and Egger tests[19] to assess potential publication bias. Additionally, we did subgroup and meta-regression analyses to assess the influence of study location (low-income and middle-income economies *vs* high-income economies), calendar effect (publication year), and small-study bias (sample size) on the pooled effect estimates. We defined significance at the α level of 0·05 for pooled adverse event estimates. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20]

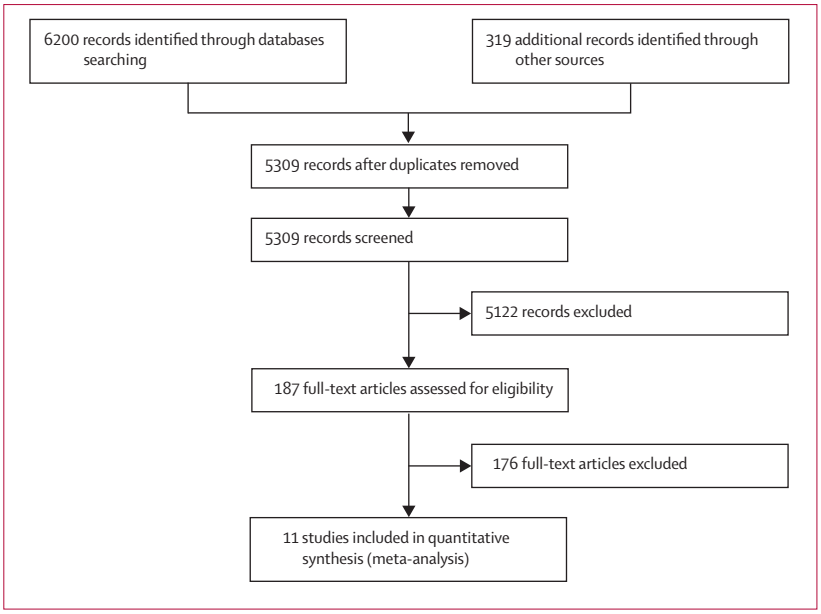

***Figure 1*: Summary of evidence search and selection**

See **Online** for appendix

For the **metaRegister of Controlled Trials** see www.isrctn.com/page/mrct

Role of the funding source

Staff (FR, SE, and MCD) of the study funder contributed to protocol development, data interpretation, and writing of the Article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search of published work yielded 5309 citations after duplicates were removed (figure 1). After review of the title and abstract, 187 full-text articles were selected for reading, and 11 studies met inclusion criteria (figure 1).[9,10,16,21–28] The studies included participants recruited during the period 1986–2012 (table 1). Three were done in the UK,[10,23,26] two in Botswana,[9,28] and one each in Brazil,[24] France,[27] South Africa,[25] and Tanzania;[16] the remaining two studies[21,22] included participants from the European Collaborative Study (ECS). The median number of HIV-infected pregnant women included in each study was 443 (range 159–8678; table 1).

	Country or region	Study period	Study design	Study setting	Study population	Sample size	ART regimen	Outcomes	Multivariate analysis
Thorne et al,[21] 2000	Europe	January, 1986–April, 2000	Prospective cohort	European Collaborative Study (ECS) and Swiss Mother+Child HIV (MoCHiV)	Infants of women with HIV	249 women on HAART (55 before conception, 194 after conception)	27% protease-inhibitor-based, 73% non-protease-inhibitor-based HAART	Preterm	Adjusted for maternal age, CD4 cell count, and type of ART
Patel et al,[22] 2005	Europe	January, 1986–December, 2003	Prospective cohort	European Collaborative Study (ECS)	Infants of women with HIV	1973 mother–child pairs; mother on HAART (789 before conception, 1184 after conception)	Protease-inhibitor-based and non-protease-inhibitor-based HAART	Congenital anomalies	Adjusted for maternal age at delivery and injection drug use during pregnancy
Martin et al,[23] 2007	UK	December, 1995–November, 2006	Prospective cohort	St Mary's General Hospital, London	Pregnant women with HIV	159 women on HAART (74 before conception, 85 after conception)	Protease-inhibitor-based and NNRTI-based HAART	Preterm	Adjusted for CD4 cell count at first visit and at delivery, viral load at first visit, zidovudine, HAART, high viral load at first visit (110 000 copies per mL), protease-inhibitor-containing regimen, and NNRTI–containing regimen
Machado et al,[24] 2009	Brazil	1996–2006	Prospective cohort	Single HIV reference centre in Rio de Janeiro Federal University	Pregnant women with HIV	443 women on HAART (130 before conception, 313 after conception)	68% protease-inhibitor-based, 32% NNRTI-based	Preterm, low birthweight	Variables with p=0·15 were included (eg, multiparity, hypertension, viral load >10 000 copies per mL, sexually transmitted infections, ART before pregnancy)
Chen et al,[9] 2012	Botswana	May, 2009–April, 2011	Prospective cohort	Six government facilities	Pregnant women with HIV	3290 women on HAART (2189 before conception, 1101 after conception)	87% zidovudine, lamivudine, and nevirapine, 9% zidovudine, lamivudine, and lopinavir-ritonavir (other 4% not reported)	Preterm, small for gestational age, stillbirth	Included covariates with a p≤0·05; risk factors for stillbirth and small for gestational age in analysis were advanced maternal age, nulliparity, maternal hypertension in pregnancy, and anaemia
Aniji et al,[25] 2013	South Africa	January, 2008–March, 2009	Retrospective cohort	Large academic obstetric unit with around 8500 deliveries per year	Pregnant women with HIV	245 women on HAART (76 before conception, 169 after conception)	96% NNRTI-based ART; 4% protease-inhibitor-based ART	Preterm	Not done, but women with multiple pregnancies and those who defaulted on ART or did not attend antenatal clinic visits, or both, were excluded from analysis
Dale et al,[26] 2013	UK	October, 1997–June, 2012	Prospective cohort	University Hospital Birmingham	All women registered with the hospital's HIV pregnancy services	180 pregnancies in women on HAART (79 before conception, 101 after conception)	HAART regimen not specified	Preterm	Adjusted for age at delivery, baseline CD4 cell count, viral load , and late presentation
Short et al,[10] 2013	UK	1996–2010	Retrospective cohort	Single hospital	Pregnant women with HIV	246 women on HAART (131 before conception, 115 after conception)	HAART regimen not specified	Preterm	Adjusted for age, race, HIV RNA baseline, CD4 cell count at baseline

(Table 1 continues on next page)

	Country or region	Study period	Study design	Study setting	Study population	Sample size	ART regimen	Outcomes	Multivariate analysis
(Continued from previous page)									
Li et al,[16] 2016	Tanzania	2004–11	Prospective cohort	Ten HIV care and treatment centres	Pregnant women with HIV	1094 women on HAART (582 before conception, 512 after conception)	80% zidovudine, lamivudine, and nevirapine, 11% stavudine, lamivudine, and nevirapine, and 3% zidovudine, lamivudine, and, efavirenz (other 6% not reported)	Preterm delivery, very preterm delivery, small for gestational age, severely small for gestational age, low birthweight, and very low birthweight	Adjusted for age, facility type, year of delivery, short stature, CD4 cell count, haemoglobin, AIDS-defining illnesses, tuberculosis history, and pregnancy-induced hypertension
Mandelbrot et al,[27] 2015	France	2000–11	Prospective cohort	The French Perinatal Cohort	Pregnant women with HIV	8678 women on HAART (4095 before conception, 4583 after conception)	81% protease-inhibitor-based, 11% NNRTI-based HAART (other 8% not reported)	Preterm, very-preterm, stillbirth	Not reported
Zash et al,[28] 2016	Botswana	2009–11	Retrospective cohort	Two largest public maternity wards	Pregnant women with HIV	2980 women on HAART (2171 before conception, 809 after conception)	Tenofovir, emtricitabine, and efavirenz vs non-tenofovir-based three-drug HAART	Preterm	Not reported

ART=antiretroviral therapy. HAART=highly-active antiretroviral therapy. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 1: **Summary characteristics of included studies (ART before conception vs ART after conception)**

Prematurity was reported in ten studies.[9,10,16,21,23–28] ART initiation before conception was associated with significantly higher risk of prematurity than ART initiation after conception (pooled RR 1·20, 95% CI 1·01–1·44; figure 2). Between-study heterogeneity was significant (I^2=77%, 95% CI 57·3–87·4; p=0·0001), suggesting that about three-quarters of the variability in the measures of the association is due to heterogeneity between studies rather than chance (figure 2). Subgroup analysis showed that the magnitude of the association was higher and significant in studies done in low-income and middle-income countries (pooled RR 1·41, 95% CI 1·22–1·63) than in those done in high-income countries, where the association was not significant (0·89, 0·54–1·47; figure 2). However, these between-group differences were not significant (p=0·0857).

Our funnel plot seems symmetric, suggesting no evidence of publication bias (p=0·480 for Egger's regression asymmetry test; figure 3). Meta-regression analysis showed that publication year (ratio of RR 1·01, 95% CI 0·93–1·10; p=0·736) and sample size (1·04, 0·91–1·18; 0·558) were not significantly associated with the pooled risk ratio of the association.

Very preterm delivery was reported as an outcome in two studies.[16,27] Initiation of ART before conception was associated with significantly higher risk of very preterm delivery than was ART initiation after conception (pooled RR 1·53, 95%CI 1·22–1·92, I^2=23%; figure 4). The same two studies included low birthweight as an outcome.[16,27] Pregnant women with HIV who started taking ART before conception were 30% more likely to have given birth to infants of low birthweight than were those who initiated ART after conception (pooled RR 1·30, 95% CI 1·04–1·62; figure 4).

The frequency of very low birthweight, which was an outcome in one study,[16] did not differ significantly between women who initiated ART before conception and those who began ART after conception (pooled RR 0·18, 95% CI 0·02–1·51; figure 4). Small for gestational age was an outcome in two studies,[9,16] and severe small for gestational age was an outcome in one.[16] The overall risk of small for gestational age (1·13, 95% CI 0·94–1·35) and severe small for gestational age (1·09, 0·82–1·45) did not differ significantly between women who began ART before conception and those who did so after conception (figure 4). Two studies reported stillbirth[9,27] as an outcome: the risk of stillbirth in women who initiated ART before conception was not significantly different from that in women who began ART after conception (1·30, 0·99–1·69, I^2=0%; figure 4). Congenital anomalies was an outcome in one study.[22] The overall risk of congenital anomalies did not differ significantly between women who initiated ART before conception and those who began ART after conception (1·24, 0·61–2·49; figure 4). 14 (1·8%) of 789 pregnant women with HIV who initiated ART before conception gave birth to infants with congenital anomalies, compared with

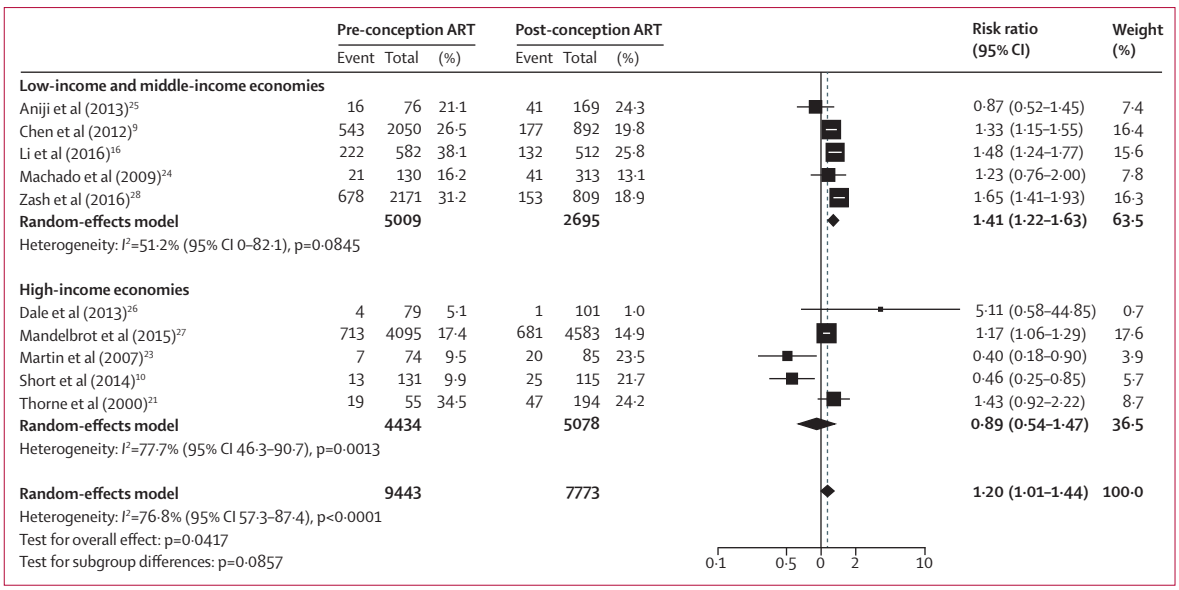

***Figure 2*: Forest plot of risk of preterm birth before 37 weeks (prematurity) in women with HIV who initiated ART before conception versus women who initiated ART after conception**

Error bars are 95% CIs. Area of boxes represents the weight given to the study. The diamond represents the overall pooled effect. The width of the line shows the 95% CIs of the effect estimate of individual studies. The width of the diamond shows the 95% CIs for the overall pooled effect estimate. ART=antiretroviral therapy.

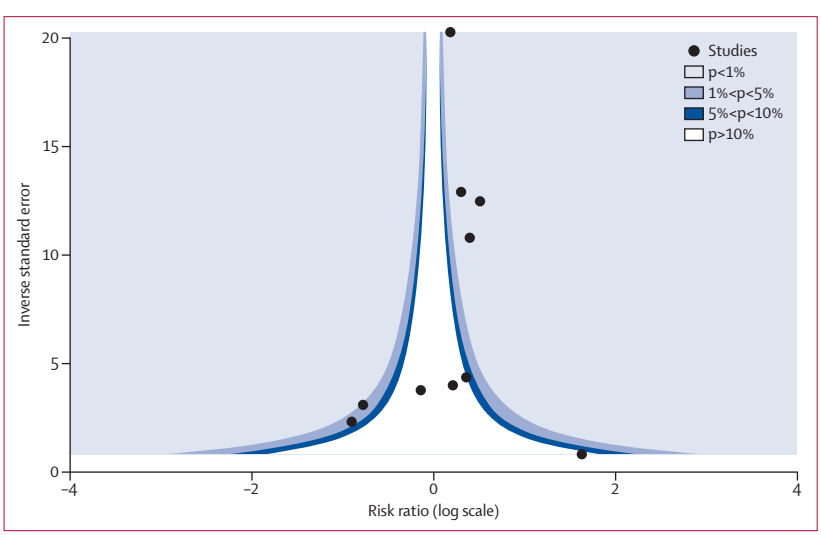

***Figure 3*: Contour-enhanced funnel plot of publication bias**

p=0·48 for Egger's regression asymmetry test.

17 (1·4%) of 1184 women who initiated ART after conception (figure 4).

None of the studies included maternal mortality as an outcome. Only one included neonatal mortality: Chen and colleagues[9] reported that 2·3% of infants born to women with HIV died in the neonatal period. Neonatal mortality did not differ significantly between women who initiated ART before conception and those who started ART after conception (2·0% *vs* 2·3%; p=0·41). The median gestational age of infants who died was 30 weeks (IQR 26–37); preterm infants had a significantly higher risk of neonatal death than did those born at term (7% *vs* 0·8%; p=0·0001). Similarly, infants who were small for gestational age had significantly higher risk of neonatal death than infants born at a birthweight expected for their gestational age (3·5% *vs* 1·5%, p=0·0001). Another risk factor for neonatal death in Chen and colleagues' analysis[9] was maternal hypertension (3·5% *vs* 1·5% for normotensive women; p=0·0002). Maternal CD4 T-cell count was not associated with risk of neonatal death (2·0% with CD4 cell count <200 cells per μL *vs* 1·8% with >200 CD4 cells per μL; p=0·71).

On the basis of the GRADE approach, we judged the quality of the evidence to be low (for prematurity) to very low (for low birthweight, small for gestational age, stillbirth, and congenital abnormalities), reflecting that confidence in the estimates of effect are uncertain and further research could change these estimates (table 2).

Discussion

In our systematic review and meta-analysis, preterm delivery, very preterm delivery, and low birthweight were significantly more common in pregnant women with HIV who initiated ART before conception than in women who first initiated ART after conception. On subgroup analysis, the magnitude of these associations was highest in studies done in low-income and middle-income countries (data not shown), where background rates of preterm delivery and low birthweight are higher than in high-income countries. Before the ART era, studies of the association between HIV infection and adverse pregnancy outcomes showed that HIV infection was significantly

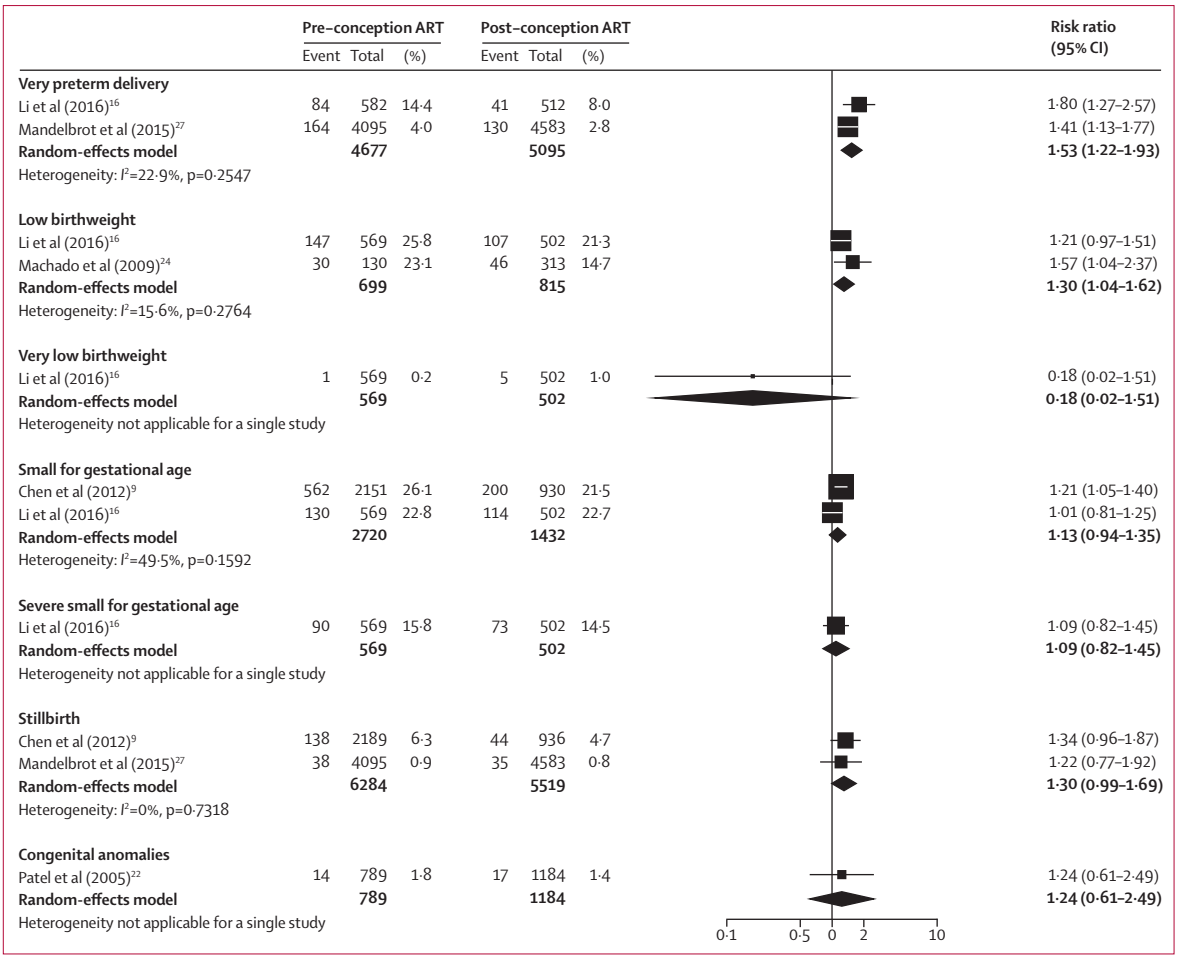

***Figure 4*: Forest plot of risk of adverse outcomes in women with HIV who initiated ART before conception versus women who initiated ART after conception (and their offspring)**

Error bars are 95% CIs. Area of boxes represents the weight given to the study. The diamond represents the overall pooled effect. The width of the lines shows the 95% CIs of the effect estimate of individual studies. The width of the diamond shows the 95% CIs for the overall pooled effect estimate. ART=antiretroviral therapy.

associated with adverse outcomes in low-income but not high-income countries.[29]

Although the results of some studies have suggested that increased risk of preterm delivery is confined to protease-inhibitor-based ART,[12–15] a range of regimens were used in the studies included in our review. For example, in Chen and colleagues' study,[9] which included 3290 pregnant women with HIV receiving ART (2189 started before conception and 1101 started after conception), 2851 (87%) women were receiving nevirapine-based ART and only 312 (9%) were receiving protease-inhibitor-based ART (24 initiated before conception, 278 initiated after conception). Similarly, in the study[16] by Li and colleagues, 91% of women were receiving nevirapine-based ART, and 3% efavirenz-based ART.

Very few data were available for comparison of pregnancy outcomes between women initiating ART before conception and those beginning ART after conception. Until 2013, in low-income settings, where the largest proportion of women with HIV reside, WHO guidelines recommended use of ART during pregnancy only for pregnant women with low CD4 cell counts (<350 cells per μL) or advanced disease. Thus, the number of women who conceived while taking ART was low. In high-income settings, where ART was recommended for all pregnant women living with HIV, until 2015 many women with high CD4 cell counts (>500 cells per μL) stopped ART after delivery.

A potentially important source of bias is that women initiating ART before conception could have risk factors for adverse pregnancy outcomes not present in women first initiating ART after conception. For example, women initiating ART before conception might be older, more likely to be multigravidae, and more likely to have been initiated on ART because they were sick than women who start ART after conception, who might be more likely to be younger, healthier primigravidae who do not require ART for their own health. In Chen and

	Anticipated absolute effects*		Risk ratio (95% CI)	Participants, n (studies)	Quality of evidence (GRADE)
	Risk with ART started after conception per 1000 women	Risk with ART started before conception per 1000 women (95% CI)			
Prematurity (born alive before 37 weeks of pregnancy are completed)	170	203 (171–244)	1·20 (1·01–1·44)	17 216 (ten observational studies)	Low†
Low birthweight (<2500 g)	188	244 (195–307)	1·30 (1·04–1·62)	1514 (two observational studies)	Very low‡
Small for gestational age (birthweight less than the 10th centile for gestational age)	219	248 (206–296)	1·13 (0·94–1·35)	4152 (two observational studies)	Very low‡
Stillbirth (born with no signs of life at or after 28 weeks' gestation or miscarriage)	14	19 (14–24)	1·30 (0·99–1·69)	11 803 (two observational studies)	Very low‡
Congenital anomalies	14	18 (9–36)	1·24 (0·61–2·49)	1973 (one observational study)	Very low‡

According to the GRADE Working Group grades of evidence, evidence is of high quality when confident that the true effect lies close to that of the estimate of the effect, of moderate quality when moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), of low quality when confidence in the effect estimate is limited (the true effect could be substantially different from the estimate of the effect), and of very low quality when there is very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect). GRADE=Grading of Recommendations Assessment, Development and Evaluation. *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †Inconsistency rated serious because heterogeneity in treatment effect estimates was substantial (I^2>50%). ‡Inconsistency rated very serious because heterogeneity in treatment-effect estimates was substantial (I^2>75%); imprecision was rated serious because of the small number of studies (smaller than the optimal information size).

***Table 2*: GRADE summary of finding, by outcome**

colleagues' Botswanan study,[9] compared with those who initiated ART after conception, women on ART before conception were more likely to be older (32 years *vs* 29 years, respectively), to be multigravidae (67% *vs* 47%), and to have a history of adverse pregnancy outcome (18% *vs* 13%). However, CD4 cell counts in the women starting ART before conception were higher than were those in women starting ART after conception (384 cells per μL *vs* 225 cells per μL; proportion with <200 CD4 cells per μL 2% *vs* 28%), and difference between the two groups in other risk factors for adverse pregnancy outcomes (such as rates of syphilis or smoking) were not noted. Additionally, multivariate analyses that controlled for risk factors such as maternal age, parity, illicit drug use, and CD4 cell count were done in several of the larger studies,[9,16,21,24] and associations were still significant. However, residual unmeasured confounding could still exist.

Another potential bias is that women who start ART very late in pregnancy (eg, after 36 weeks' gestation) do not have the same opportunity for a preterm delivery as those starting earlier or before conception. However, in most studies, pre-conception and post-conception initiation of ART were compared without taking into account the gestational week that ART was begun, and median gestational age for those starting ART during pregnancy was not provided.

Strengths of our meta-analysis include the use of a predefined protocol, a comprehensive search strategy, and involvement of two independent reviewers in all stages of the review process. To our knowledge, ours is the first systematic review in which measures of adverse pregnancy outcomes in women with HIV were pooled to address specifically associations with initiation of ART before conception.

Our study also has some limitations. The review was limited by the scarcity of studies reporting most of the outcomes of interest. Although we examined for publication bias, we recognise that publication bias is always present when investigating routine outcomes from interventions widely provided in non-research settings. Also, all studies included were observational, which could lead to bias as a result of unmeasured confounding.

Several published studies did not differentiate women initiating ART before conception from those initiating ART during the first trimester, and hence could not be included in our analysis. For example, a previous meta-analysis[30] published in 2007 showed that ART use after conception did not increase preterm delivery overall, but initiation of combination ART before pregnancy or in the first trimester resulted in an increased risk of preterm delivery (odds ratio 1·71, 95% CI 1·09–2·67) compared with initiation in the second or third trimester. The authors noted that increased surveillance is needed to quantify this risk accurately.

Additionally, in some studies, pre-conception initiation of ART was compared with initiation of various regimens during pregnancy, including zidovudine single-drug prophylaxis, and thus could not be included in our analysis. For example, in their large French study,[11] Sibiude and colleagues reported increased rates of preterm delivery in women who began ART before conception compared with women starting antiretroviral regimens during pregnancy. However, this study included use of zidovudine alone or dual antiretroviral

prophylaxis.[11] The Antiretroviral Pregnancy Registry compares use of different antiretroviral drugs in the first trimester with use in the second or third trimester, but does not provide data for pre-conception use or by type of regimen.[31]

Few investigators differentiated between very preterm delivery (<34 weeks' gestation) and preterm delivery (34–37 weeks' gestation),[16,27] or between very low birthweight (<1500 g) and low birthweight.[16] Severe prematurity and low birthweight are associated with significantly more infant morbidity and mortality than are more moderate prematurity and birthweight. Additionally, reports of neonatal and infant mortality were lacking from all but one study. In Chen and colleagues' report,[9] ART initiation before conception was not associated with increased neonatal mortality compared with ART initiation after conception, despite being associated with higher risks of prematurity and low birthweight. Finally, spontaneous preterm delivery was not differentiated from induced prematurity (induction of labour or caesarean section for complications) in any of the included studies.

The benefits of ART for prevention of mother-to-child transmission of HIV and for maternal health clearly outweigh any risks identified so far, and there is no question that ART should be initiated in all pregnant women and continued thereafter. Nevertheless, further research is needed to define these risks better and to determine how to optimise ART to allow safe, healthy pregnancies for women with HIV and good health outcomes for both mother and child. With recommendations for immediate initiation of ART after HIV diagnosis and 1·5 million pregnancies annually in women with HIV, fetal exposure to ART begun before conception will increase. Therefore, better monitoring of adverse pregnancy outcomes is essential to determine whether these outcomes are more common in people with HIV than in those without HIV. More research is needed to investigate causal mechanisms for adverse pregnancy outcomes with ART use to establish if modifiable factors could be exploited to reduce or prevent such outcomes.[32,33] Differences in pregnancy outcomes between ART regimens need to be established, and a better understanding is needed of the ultimate effect of such outcomes on maternal, neonatal, and infant morbidity and mortality.

Contributors

OAU assisted with protocol development, extracted data, did data synthesis, interpreted results, and drafted and revised the Article. JBN assisted with protocol development, drafting and revisions of the Article, and data analysis and interpretation. JA was involved in writing the Article and data interpretation. EJM obtained grant funding and assisted with protocol development, interpretation of results, and drafting of the Article. LMM assisted with the protocol design, writing of the Article, revisions, and data interpretation. SK, FR, SE, and MCD were involved in the concept, design, interpretation, and writing of the Article. All authors approved the final submitted version.

Declaration of interests

We declare no competing interests.

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