International Journal of Antimicrobial Agents 62 (2023) 106823

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

# Maternal antiretroviral treatment for HIV infection and risk of small-for-gestational-age birth: A systematic review and meta-analysis of protease inhibitor-based treatment and timing of treatment

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ARTICLE INFO

*Article history:*
Received 16 January 2022
Accepted 17 April 2023

Editor: Professor Philippe Colson

*Keywords:*
HIV
Pregnancy
Protease inhibitor
cART initiation
SGA

ABSTRACT

*Background:* Data indicate that certain combination antiretroviral treatment (cART) regimens, particularly protease inhibitor (PI)-based regimens, and cART initiation before conception may be associated with adverse pregnancy outcomes. The risk of having a small-for-gestational-age (SGA) infant was examined among pregnant HIV-infected mothers on 1) PI-based compared to non-PI-based cART, and 2) any cART initiated before compared to after conception.

*Methods:* A search was conducted using PubMed, Embase, and the Cochrane Library, and a systematic review was performed of studies published since Dec 1, 1995. Effect estimates with 95% confidence intervals (CIs) were extracted and meta-analyses with random-effects models were conducted. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation tool.

*Findings:* Of 783 identified studies, 28 fulfilled the inclusion criteria. Meta-analysis indicated that PI-based cART was associated with a possible slightly increased risk of SGA compared with non-PI-based cART (pooled odds ratio [OR]: 1·09; CI: 0·76, 1·55). Initiation of cART before conception was also associated with a possible slightly increased risk of SGA compared with after conception (pooled OR: 1·08; CI: 0·95, 1·22). The overall certainty of evidence was very low and low for the first and second research questions, respectively.

*Interpretation:* Although the benefits of cART largely outweigh the risks, these findings indicate the possibility of slightly increased risks of having an SGA infant. This indicates that careful monitoring of fetuses exposed to PI-based cART or cART before pregnancy might be reasonable. Based on the uncertainty of evidence, further research may change this conclusion.



## 1. Introduction

Over the last few decades, there has been a continuous roll-out of interventions to prevent HIV transmission and to reduce adverse health outcomes among those infected with this virus [1–10]. Combination antiretroviral treatment (cART), consisting of three drugs in combination, is probably the single most important intervention. cART was introduced in the mid-1990s [11] and since then has been the recommended treatment regimen, due to rapid development of drug resistance with monotherapy regimens [12]. The mother-to-child transmission rate of HIV among women who start cART before conception is observed to be near zero [13], compared with 15–45% among women without such therapy [14]. The estimated percentage of pregnant women living with HIV who received antiretrovirals for preventing mother-to-child transmission increased from 45% in 2010 to 85% in 2020 [15]. The antiretroviral treatment coverage among all people living with HIV was only 4% in 2003 and increased to 73% in 2020 [16].

The recommended drug combinations include either three nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) or a dual nucleoside reverse transcriptase inhibitor (NRTI) component as backbone and a third agent as base, such as a non-NRTI (NNRTI), a protease inhibitor (PI), or an integrase inhibitor [1–10]. Eligibility criteria, based on CD4 cell levels and clinical stage, have changed over the years.

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https://doi.org/10.1016/j.ijantimicag.2023.106823

Maternal HIV infection is associated with an increased risk of preterm delivery, a low birth weight infant, a small-for-gestational-age (SGA) infant, and stillbirth [17].

In addition, exposure to cART during pregnancy has been reported to increase the risk of preterm delivery and low birth weight compared with monotherapy, but the evidence is mixed [18–26]. Regimens based on PIs, particularly ritonavir-boosted PI therapy, have been reported to be associated with an increased risk of preterm delivery compared with monotherapy or non-boosted triple therapy [19,20,23,24,26]. Also, initiating cART before compared with after conception has been associated with an increased risk of preterm delivery and low birth weight [27]. Recently published systematic reviews have shown that PI-based cART is associated with an increased risk of SGA compared with non-PI-based cART (odds ratio (OR) 1·24, 95% confidence interval (CI) 1·08, 1·43) [28], whereas the risk of SGA is more uncertain when comparing any cART initiated before conception with after conception (OR 1·13, CI 0·94, 1·35, and OR 1·04, CI 0·83, 1·30 in two recent reviews) [27,29].

Fetal growth restriction is defined as failure of the fetus to meet its growth potential, most commonly as a result of placental dysfunction, and it contributes to stillbirths and neonatal mortality [30]. However, to measure fetal growth restriction is complex and ideally includes a combination of measurements of fetal size and Doppler abnormalities. Also, fetal growth restriction should ideally be classified into early-onset (<32 weeks) or late-onset (≥32 weeks), as early-onset cases can have other causes and are more often severe compared with late-onset cases. Ultrasound-based markers and multiparameter algorithms are not recommended for universal screening of fetal growth restriction, as they only have a moderate predictive accuracy for this measure. The International Federation of Gynecology and Obstetrics (FIGO) recommends performing a risk stratification for fetal growth restriction using history-based risk factors. In settings with poor access to advanced medical technology, ascertainment of SGA based on birth weight and gestational age often serves as an estimate for fetal growth restriction.

Placental insufficiency has been suggested as the most important explanation for fetal growth restriction in infants born to HIV-positive women on cART [31]. PI-based cART may influence placenta vascular formation and might be associated with decreased progesterone levels [31,32]. This might in turn contribute to fetal growth restriction. HIV infection may also result in vascular damage and placental insufficiency [33].

SGA is an important outcome and fetuses with growth restriction may require increased surveillance during pregnancy [34]. Studies of SGA could also contribute to knowledge about the etiology of adverse birth outcomes in women on cART.

A systematic review and meta-analysis was conducted to summarize published data on the risk of giving birth to an SGA infant for women receiving cART with a PI during pregnancy compared to those receiving cART without a PI. The risk of giving birth to an SGA infant when cART was initiated before compared to after conception was also examined. Several systematic reviews have included SGA in their analyses [19,23,27–29,35], but in contrast to these, the current analyses also examined whether the effect sizes differed depending on exactly which cART regimens were included in the exposure and reference groups.

## 2. Methods

### 2.1. Search strategy and selection criteria

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [36]. An electronic search was first performed on October 19, 2021, in the databases PubMed, Embase, and the Cochrane Library. An updated search was performed on December 10, 2022. The search combined MeSH terms and free-text terms. The MeSH terms consisted of the following four elements: “Anti-HIV agents”/”Anti human immunodeficiency virus agent”, “HIV infections”/”Human immunodeficiency virus infection”, “Pregnancy outcome” and “Infant, small for gestational age”/”Small for date infant”. Various free-text search terms for the four elements were used. The search was restricted to publication dates after December 1, 1995, as this was the month of approval of the first PI [37]. Conference abstracts, papers and posters were reviewed. The reference lists of relevant systematic reviews and articles were also reviewed to identify other studies on the same topic. See the Supplementary Materials for details on the search strategy.

The research questions and methods were specified in advance in a protocol published in the International prospective register of systematic reviews (PROSPERO, number CRD42020218091). For the first research question, studies had to provide data for both pregnant women receiving cART with a PI and pregnant women receiving cART without a PI. For the second research question, only studies with data from both women who initiated cART before conception and women who initiated cART after conception were included. For both research questions, only studies that defined SGA as birth weight below the 10th percentile according to gestational age were included. Some papers did not specify whether all the women were on cART. Only those studies in which it appeared highly probable that nearly all the women included were on cART were considered for the analysis. Case reports, comments, and letters were excluded, and only papers written in English or Scandinavian languages were included. The first screening focused on the title and abstract of the papers, and if they clearly did not fulfil the above criteria, they were excluded. This was followed by a full-text screening of potentially relevant papers to determine which studies should be included in the systematic review. Both stages of the screening process were conducted independently by two of the authors (TR and IFS). All ambiguities were discussed, and corresponding authors of the studies were contacted when clarification was needed.

### 2.2. Data analysis

Information on study characteristics (Table 1), sample size for SGA and drug details (Tables S1 and S2) were extracted from the included studies. Either crude or adjusted effect estimates were extracted independently from the papers by two of the authors (TR and IFS). If only descriptive statistics were reported, crude effect estimates were calculated. If more than one exposed or reference group was relevant to include from the same study, effect estimates for both comparisons were extracted, and details for each comparison are described in the corresponding forest plot as well as in Tables S1 and S2. Predefined criteria, based on drug types and adjustment for potential confounders, determined which effect estimates were included in the main meta-analysis (analysis 1·1 and 2·1) and sensitivity analyses (1·2, 1·3, 1·4, 2·2, 2·3, 2·4 and 2·5) for each research question, except for analysis 2·2, where the criteria were adjusted post hoc because there were few eligible studies (Supplementary Materials, Tables S1 and S2). Adjusted effect estimates were generally preferred before crude estimates from the same study, except for sensitivity analyses 1·4 and 2·5, where the effect estimates based on the highest number of observations from each study were preferred. For the research question comparing PI-based cART with non-PI-based cART, the criteria for inclusion in the main meta-analysis were that the estimates should be adjusted for potential confounders and >80% of the reference group should be on NNRTI-based cART. For the research

**Table 1**
Summary characteristics of included studies.

| | Country or region | Study design | Study period | Adjustment in multivariable analyses | Missing observations for SGA, type of cART regimen, and adjustment variables[a] |
|---|---|---|---|---|---|
| Aaron et al. [49] | USA, Philadelphia | Prospective cohort study | January 2000-January 2011 | Adjusted for maternal age, race, smoking, education, viral load, CD4 count, medication, and timing of initiation | SGA and type of cART regimen: 0% |
| Balogun et al. [44] | Canada, Toronto | Prospective cohort study | September 2010-December 2015 | Only data for crude estimate extracted | SGA: 1·6% |
| Brandon et al. [42] | United Kingdom, Oxford | Retrospective cohort study | January 2008-October 2019 | Only data for crude estimate extracted | SGA: 0%, type of cART regimen: 3% (based on available numbers for final cART regimen) |
| Chen et al. [25] | Botswana | Retrospective cohort study | 2009-2011 | Covariates with a significance level ≤0·05 and CD4 count were included in the model. Additional risk factors for stillbirth and SGA in multivariate analysis were advanced maternal age, nulliparity, maternal hypertension in pregnancy, and anemia | SGA: 1%, type of cART regimen: 4%, CD4 count: 51% |
| Chetty et al. [57] | South Africa, KwaZulu-Natal | Retrospective cohort study | January 2010-December 2015 | Only data for crude estimate extracted | SGA and type of cART regimen: 0% |
| Delicio et al. [47] | Brazil, Campinas | Retrospective cohort study | 2000-2015 | Only data for crude estimate extracted | SGA: 1·8%, type of cART regimen: 0% |
| Ejigu et al. [52] | Ethiopia, Addis Ababa | Retrospective cohort study | February 2010-October 2016 | Adjusted for maternal age, weight, marital status, education, parity, CD4 cell count during pregnancy, and WHO clinical stage during pregnancy. Models comparing different cART regimens were adjusted for timing of treatment initiation | SGA: 0%, type of cART regimen: 0%, maternal age: 1·7%, weight: 11·0%, marital status: 1·4%, education: 30·6%, parity 7·8%, CD4 count: 10·8%, WHO clinical stage: 4·0% |
| The EPPICC[b] Study Group, 2019 [58] | Eight European countries[c] | Retrospective cohort study | 2008-2014 | Only data for crude estimate extracted | SGA: 1·4%, type of cART regimen: 0% |
| Favarato et al. [59] | United Kingdom and Ireland | Prospective cohort study | 2007-2015 | Only data for crude estimate extracted | SGA: 6·0%, type of cART regimen: 0% |
| Floridia et al. [60] | Italy | Retrospective cohort study | January 2008-2018 | Only data for crude estimate extracted | SGA: ≤10%, type of cART regimen: 0%. |
| Hung et al. [43] | Taiwan, Northern | Retrospective case-control study | January 2011-December 2018 | Only data for crude estimate extracted | SGA and type of cART regimen: 0% |
| Li et al. [21] | Tanzania, Dar es Salaam | Prospective cohort study | November 2004-September 2011 | Only data for crude estimate extracted | SGA: 2·1%, type of cART regimen: 0·9% |
| Lopez et al. [61] | Spain, Barcelona | Prospective cohort study | January 2006-December 2011 | Only data for crude estimate extracted | SGA and type of cART regimen: 0% |
| Malaba et al. [50] | South Africa, Cape Town | Prospective cohort study | April 2013-August 2015 | Adjusted for maternal age, maternal height, parity, previous preterm delivery, CD4 count, and viral load | SGA: 14·6%, type of cART regimen: 14%, height: 16%, other adjustment variables: <3% |
| Moseholm et al. [51] | Denmark | Retrospective cohort study | January 2000-December 2019 | Adjusted for maternal age, maternal region of birth, year of birth, mode of delivery, illicit drug or alcohol use, smoking, maternal comorbidity, maternal CD4 count, HIV RNA at delivery. All models were adjusted for intragroup correlations in children born to the same mother | Gestational age: 1%, birth weight: 1%, type of cART regimen: 0%, maternal age: 0%, maternal region of birth: 0%, year of birth: 0%, mode of delivery: 1%, illicit drug or alcohol use: 6%, smoking: 7%, maternal comorbidity: 0%, maternal CD4 count: 1%, HIV RNA at delivery: 1% |
| Nyemba et al. [62] | South Africa, Cape Town | Prospective cohort study | January 2017-July 2018 | Only data for crude estimate extracted | SGA: 0%, type of cART regimen: 20% |
| Patel et al. [45] | United States and Puerto Rico | Retrospective cohort study | April 2007-January 2020 | Adjusted for age at conception, race, ethnic group, educational attainment, timing of maternal HIV infection diagnosis, trimester at the first prenatal care visit, pre-conception or post-conception initiation of cART, use of tobacco during pregnancy, use of alcohol during pregnancy, use of other substances during pregnancy, any sexually transmitted infection or vaginitis during pregnancy | SGA and type of cART regimen: 0% |

(*continued on next page*)

**Table 1** (*continued*)

| | Country or region | Study design | Study period | Adjustment in multivariable analyses | Missing observations for SGA, type of cART regimen, and adjustment variables[a] |
|---|---|---|---|---|---|
| Quinn et al. [54] | Tanzania, Dar er Salaam | Prospective cohort study | June 2015-September 2019 | Adjusted for CD4 count, WHO disease stage, self-reported history of hypertension, any alcohol use (in the last month), body mass index at randomization, parity, maternal age, maternal education, marital status, wealth quintile, clinic site, whether they received vitamin D or placebo | SGA: 6·3%, type of cART regimen: 0·1%. A missing indicator was used to account for those who were missing maternal CD4 count (number not reported). For all other covariates: Low levels (<5% for each covariate) of unavailable covariate information |
| Ramokolo et al. [56] | South Africa | Cross-sectional study | October 2012-May 2013 | Adjusted for syphilis serology, tuberculosis during pregnancy, maternal age, parity, maternal education, ANC visits, household socio-economic quintile, household food insecurity, infant race, infant gender | SGA: 26·8%, type of cART regimen: 0%, syphilis serology: 29·6%, tuberculosis: 3·0%, maternal age: 0·2%, parity: 2·8%, education: 0·2%, ANC visits: 31·8%, infant race: 1·3%, other adjustment variables: 0% |
| Rempis et al. [63] | Uganda, Fort Portal | Cross-sectional study | February 2013-December 2013 | Only data for crude estimate extracted | SGA: 3·2%, type of cART regimen: 0% |
| Santosa et al. [48] | South Africa, Soweto | Prospective cohort study | May 2013-July 2016 | Adjusted for maternal age, education, marital status, smoking, alcohol consumption, socioeconomic status, pre-pregnancy BMI, parity, history of stillbirth, history of preterm birth, history of low birth weight, and history of neonatal death. Analyses with inclusion of CD4 cell count during pregnancy were also performed. | Gestational age: 7%, birth weight: 8%, type of cART regimen: 0%, other variables: <8% missing |
| Snijdewind et al. [53] | The Netherlands | Retrospective cohort study | January 1997-February 2015 | Variables with a p-value of ≤0·10 in the univariate analyses were included in the multivariate logistic regression analysis: cART regimen, region of origin, and parity | Gestational age or birth weight: 2·2%, type of cART regimen: 0%, region of origin other than Western Europe or sub-Saharan Africa: 24·4%, parity: 2·5% |
| Tate et al. [64] | USA, Tennessee | Prospective cohort study | January 2010-March 2017 | Only data for crude estimate extracted | SGA and type of cART regimen: 0% |
| Ugochukwu et al. [65] | Nigeria, Nnewi | Retrospective cohort study | January 2009-December 2015 | Only data for crude estimate extracted | SGA and type of cART regimen: 0% |
| Van der Merwe et al. [46] | South Africa, Johannesburg | Retrospective cohort study | October 2004-March 2007 | Only data for crude estimates extracted | SGA: 27·3%, type of cART regimen: 0% (among those with known cART duration) |
| Watts et al. [26] | USA | Retrospective cohort study | 1998-October 2010 | Only data for crude estimate extracted | SGA: <4%, type of cART regimen: 0% |
| Zash et al. [55] | Botswana | Retrospective cohort study | August 2014-August 2016 | Adjusted for maternal age, gravidity, low educational attainment | SGA: 3%, type of cART regimen: 29% |
| Zash et al. [66] | Botswana | Retrospective cohort study | March 2013-August 2016 | Only data for crude estimate extracted | SGA: <3%, type of cART regimen: 0% |

SGA: Small-for-gestational-age. cART: Combination antiretroviral treatment. WHO: World Health Organization. ANC: Antenatal care. BMI: Body mass index.

[a] If missing is not presented here, the study did not specify this or we did only extract data for crude estimate.

[b] European Pregnancy and Paediatric HIV Cohort Collaboration.

[c] 45% (3207) of the pregnancies were in the United Kingdom and Ireland, 44% (3134) in Ukraine, 7% (469) in Russia, smaller numbers in Belgium, Romania, Spain and Switzerland.

question comparing timing of initiation, the main meta-analysis was restricted to studies with adjusted effect estimates and with >80% of the whole study sample being on NNRTI-based cART. Extracted risk ratios were transformed to ORs to better compare the extracted effect estimates. This was done using a method described by Zhang and Yu [38]. Effect estimates were combined using a random-effects DerSimonian-Laird model for each of the two specific research questions, producing pooled ORs with corresponding 95% CIs. ORs and CIs might differ slightly from those published in the papers due to the imputation of the standard error and the assumption of normality used in the meta-analysis. Subgroup analyses to explore differences in pooled effect estimates from studies performed in low- and middle-income countries versus high-income countries were planned if there were at least three studies in each subgroup. Statistical heterogeneity was assessed using the $I^2$ value, chi-squared test and its corresponding *P*-value. Possible small-study effects were also explored by computing contour-enhanced funnel plots and Egger regression-based tests. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [39]. Risk of bias in the estimate of SGA in each of the included studies was assessed using the Newcastle-Ottawa Scale [40], and the quality was rated as either good, fair or poor. Analyses were performed using Stata/SE version 17·0.

### 2.3. Role of the funding source

All authors have positions funded by their respective institutions, but these institutions had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the review for publication.

## 3. Results

The search resulted in 499 articles in PubMed, 484 in Embase, and 61 in the Cochrane Library, giving a total of 1044 papers (Figure 1). A total of 783 papers remained after removing duplicates. After title and abstract screening, 90 articles remained and were chosen for full-text reading. Full-text screening led to another 66 papers being excluded (Figure 1). Two articles included data from the same hospital and had overlapping study periods [41,42]; therefore, the paper by Montgomery-Taylor et al. [41] was excluded. Eight relevant systematic reviews were also identified and screened for additional references, resulting in the inclusion of three additional papers. One additional article was identified while searching the internet to find out whether the authors of a conference abstract had published a peer reviewed paper. Thus, a total of 28 papers met the inclusion criteria. A search in the reference lists of the included papers and in grey literature did not identify any other relevant studies.

Fourteen of the included studies were from sub-Saharan Africa, and 14 were from Europe, Asia, or America. All the studies were observational. There was one cross-sectional study, and 27 cohort studies, 10 of which were prospective. The study periods for the included studies ranged from 1997 to 2020 (Table 1). The included studies defined SGA based on sex-specific weight standards, except one study that did not specify this [43] and one that did not use sex-separate standards [26]. Small-for-gestational-age (SGA) analyses were assumed to include term and preterm deliveries, although this was not specified in some studies [44,45]. Malaba et al. also performed analyses that included only term infants, and timing of initiation compared with the results from these analyses did not differ (data not shown). Furthermore, most studies specified that they only included singletons in the SGA analyses, although some did not specify this [21,44,46], and three also included twins [42,45,47]. One study presented data for neonatal complications. In Delicio et al., respiratory distress (7.2%) and neurological disorders (6.7%) were the most commons neonatal complications, although these results were not stratified by any other variables, such as SGA or cART exposure [47]. Another study presented data for different congenital abnormalities, but these only constituted 11 of 633 births in total [48]. Finally, among studies where adjusted effect sizes could be extracted, some of the studies adjusted for viral load [49–51], or CD4 count [25,48–54], but most did not specify how many of the included women were already on cART when the viral load or CD4 count was measured. Moseholm et al. measured CD4 count and viral load at delivery, and the majority of women (86%) had an HIV RNA below 50 copies/mL. One study included CD4 cell count in sensitivity analyses [55]. One study adjusted for opportunistic infections. such as syphilis and tuberculosis [56].

Eighteen of the included studies evaluated the risk of giving birth to an SGA infant for pregnant women receiving cART with a PI compared to those receiving cART without a PI (Table S1). Eleven studies reported specific names of the PI drugs, the most common being atazanavir, darunavir, lopinavir, ritonavir, and nelfinavir (Table S1). Combinations of NRTIs and NNRTIs were the most common cART regimens in the reference groups, nevirapine and efavirenz in particular being used as the NNRTI base. Five effect estimates were included in the main meta-analysis, two of these from the same study, where study participants in the reference category were the same, but the exposure group differed (Figure 2). The pooled OR with corresponding 95% CI in the main meta-analysis was 1·09 (0·76, 1·55). In the sensitivity analyses, the pooled ORs increased slightly, and the corresponding 95% CIs narrowed as more effect estimates were added to the analyses (Figures S1–S3). The highest effect size was found in analysis 1·3 (OR 1·39, CI 1·14, 1·70) (Figure S2), where >80% of the women in the reference group were on NNRTI-based cART, but where crude effect sizes were also included. A subgroup analysis exploring differences in pooled effect estimates by country income level was not conducted as only two studies from high-income countries and two from low- and middle-income countries were included in the main meta-analysis.

Nineteen studies evaluated the risk of giving birth to an SGA infant when any cART was initiated before conception compared to after conception (Table S2). In the studies that reported the type of cART drugs, the majority of women were on either NRTIs, NNRTIs, or PIs. Integrase strand-transfer inhibitors were used in a few studies, and the proportions of women taking this type of drug were low. Seven effect estimates were included in the main meta-analysis, and the pooled OR and corresponding 95% CI was 1·08 (0·95, 1·22) (Figure 3). In the sensitivity analyses, the pooled ORs did not change substantially (Figures S4–S7). A slightly higher estimate was found when >50% were on PI-based cART (OR 1·26, CI 0·90, 1·76) (Figure S4), and when all cART regimens were included (OR 1·16, CI 1·03, 1·30) (Figure S5). Lower estimates were found in sensitivity analyses where crude estimates were included, regardless of cART regimen (Figure S6 and S7). A subgroup analysis was not performed by country income level as only two studies from high-income countries were included in the main meta-analysis.

The certainty of evidence was initially set to low, as all the included studies were observational studies. For the adjusted effect estimates there were no serious concerns about bias in the individual studies, except for one study for which the quality was only rated as fair [53]. For all crude effect estimates that were extracted, the risk of bias was high. In the main meta-analysis comparing cART with a PI and cART without a PI, heterogeneity between effect estimates was substantial ($I^2$=67%), with a chi-square test statistic of 12·1 and a *P*-value of 0·02 (Figure 2). The degree of heterogeneity between effect estimates was reduced in the sensitivity analyses, although it was still moderate to substantial. For the main meta-analysis comparing timing of initia-

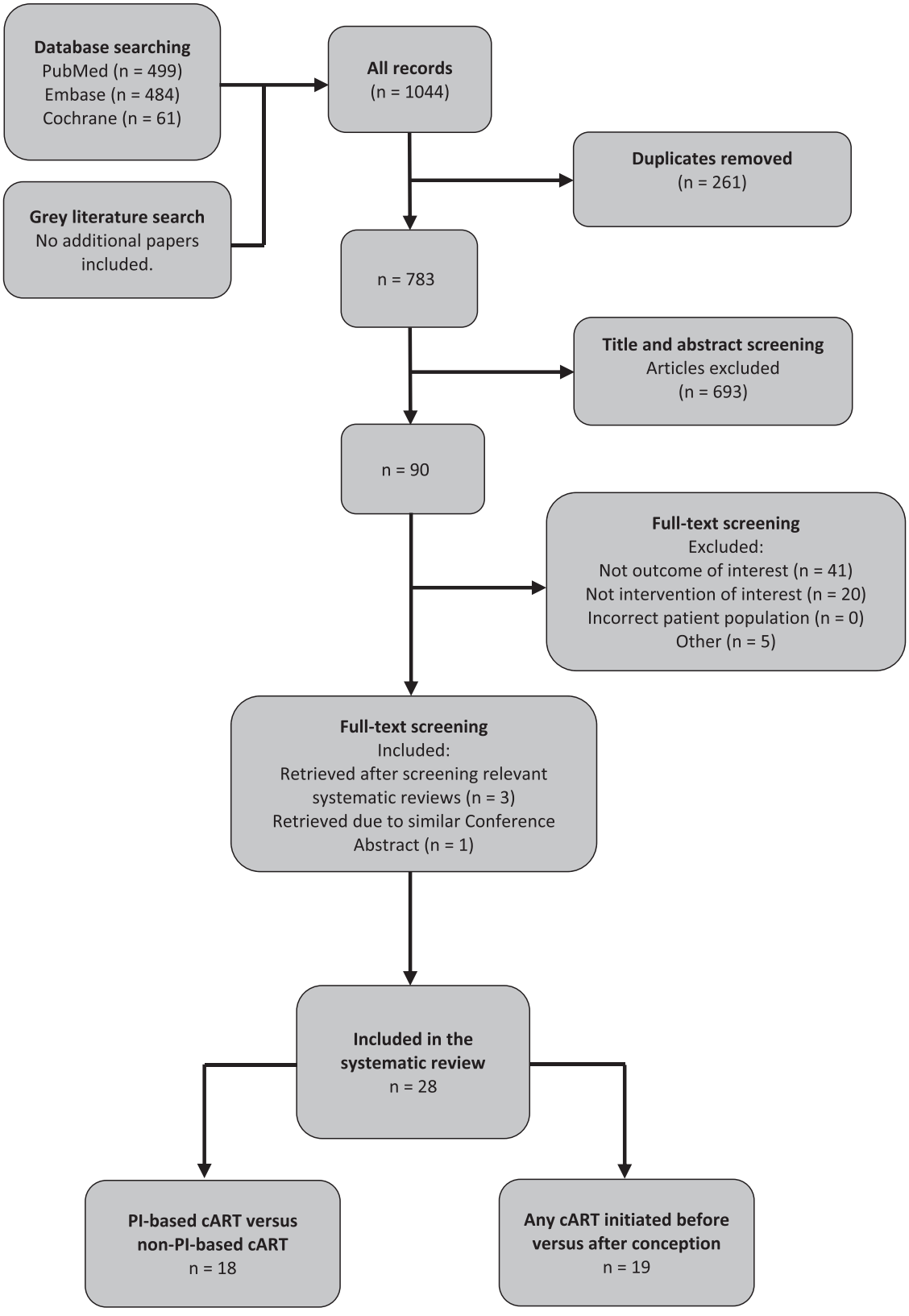


**Figure 1.** Flow diagram of search and selection process. PI: Protease inhibitor. cART: Combination antiretroviral treatment.

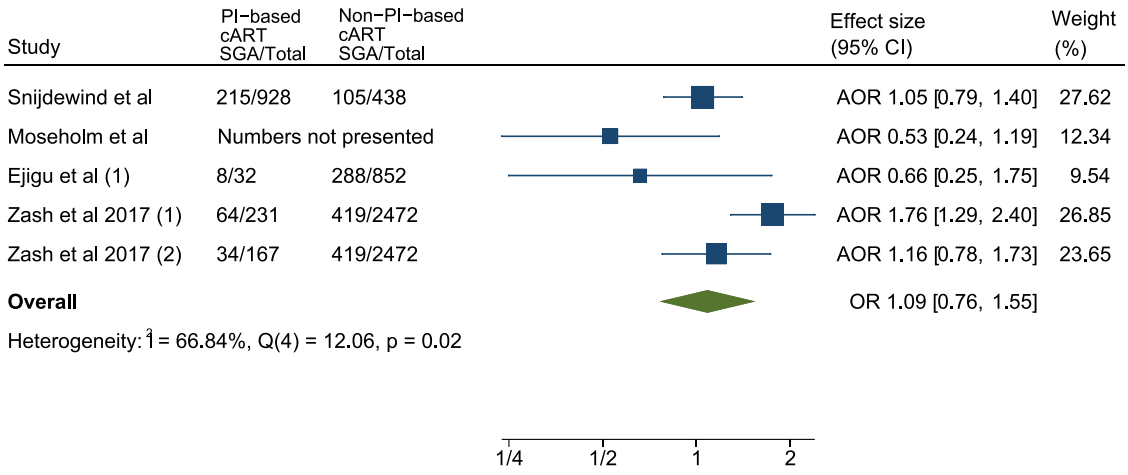


**Figure 2.** Forest plot of the risk of having an SGA infant in women on PI-based cART compared with cART without a PI. Analysis 1·1: Only adjusted affect sizes, >80% on NNRTI-based cART in reference group. Studies are listed chronologically according to first year of study period. Number in parenthesis refers to comparison number extracted from the study, as listed in Table S1: Ejigu et al. (1): PI-based compared with EFV-based cART (NNRTI-based). Zash et al. 2017 (1): TDF-FTC-LPV-r (PI-based cART) compared with NNRTI-based cART. Zash et al. 2017 (2): ZDV-3TC-LPV-r (PI-based cART) compared with NNRTI-based cART. PI: Protease inhibitor. cART: Combination antiretroviral therapy. SGA: Small-for-gestational-age. AOR: Adjusted odds ratio. OR: Odds ratio. NNRTI: Non-nucleoside/nucleotide reverse transcriptase inhibitor. EFV: Efavirenz. TDF: Tenofovir Disoproxil Fumarate. FTC: Emtricitabine. LPV-r: Lopinavir/ritonavir. ZDV: Zidovudine. 3TC: Lamivudine.

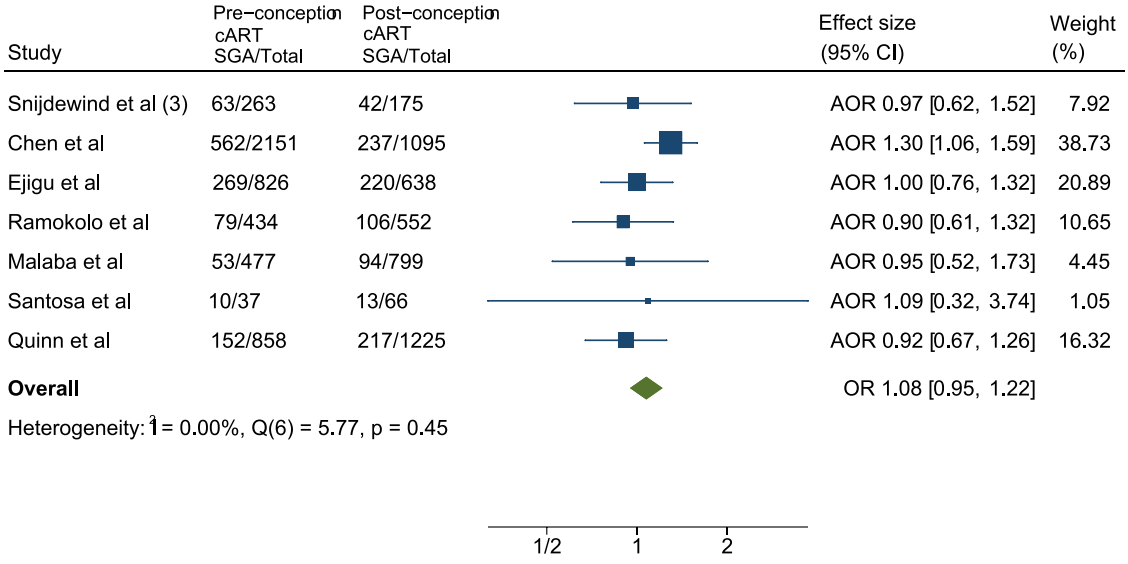


**Figure 3.** Forest plot of the risk of having an SGA infant in women on cART initiated before conception compared with after conception. Analysis 2·1: Only adjusted effect sizes, >80% on NNRTI-based cART. Studies are listed chronologically according to first year of study period. Number in parenthesis refers to comparison number extracted from the study, as listed in Table S2: Snijdewind et al. (3): NNRTI-based cART (100%). cART: Combination antiretroviral therapy. SGA: Small-for-gestational-age. AOR: Adjusted odds ratio. OR: Odds ratio. NNRTI: Non-nucleoside/nucleotide reverse transcriptase inhibitor.

tion (Figure 3), heterogeneity between effect estimates was low ($I^2$=0%), with a chi-square test statistic of 5·8 and a *P*-value of 0·45. The degree of heterogeneity between included effect estimates varied between 0% and 45% in the sensitivity analyses. Lastly, the contour-enhanced funnel plots of studies included in the main meta-analysis for each research question did not indicate any obvious presence of small-study effects (Figure S8–S9). The Egger regression-based test for studies in the main meta-analyses produced *P*-values of 0·05 and 0·20 for PI-based cART versus non-PI-based cART, and cART initiated before versus after conception, respectively.

The certainty of evidence was set to very low for studies comparing PI-based cART with non-PI-based cART. There were several reasons to downgrade based on the GRADE certainty of evidence rating above, in particular the degree of inconsistency. For studies comparing timing of initiation, the certainty of evidence was set to low, as the degree of inconsistency was smaller.

## 4. Discussion

In this systematic review and meta-analysis of SGA risk related to maternal cART, SGA was possibly a slightly more common pregnancy outcome if the mother was on cART with a PI compared with cART without a PI during pregnancy, which adds to the previously described increased risk of preterm delivery [19,20,23,24,26,28]. The systematic review by Cowdell et al. included many of the papers that are in the current systematic review, and showed an increased risk of SGA when comparing PI-based cART with non-PI-based cART [28]. However, these authors did not restrict the analysis to only adjusted estimates or only NNRTI-based cART in the reference group, as was done in the main meta-analysis for the current work (Figure 2). When crude estimates and all non-PI-based cART regimens were included in the reference group (Figure S2 and S3), the current study estimates better approximated the estimate reported by Cowdell et al.

There might be a slightly higher risk of SGA if maternal cART is initiated before compared with after conception. The pooled OR from the current main meta-analysis closely approximates the pooled estimates from two other systematic reviews on the risk of SGA [27,29], particularly in sensitivity analyses, where crude estimates and all cART regimens were also included in the current work. The current analyses showed a tendency towards a higher risk of SGA when only adjusted effect sizes were included, and this finding might strengthen the conclusion that there is a slightly higher risk of SGA in these pregnancies.

Unfortunately, it was not possible to examine the effect of ritonavir-boosted PI compared with non-boosted PI on the risk of SGA, as there were no studies that explicitly mentioned that the proportion on ritonavir-boosted PI was low.

Some of the possible causes of fetal growth restriction, including PI-based cART, placental changes, and decreased progesterone levels [31,32,67], may also be causes of preterm deliveries. Low progesterone levels might be associated with preterm delivery [68]; therefore, progesterone supplementation is recommended during pregnancy to reduce the risk of recurrent preterm delivery [69]. Progesterone supplementation is also shown to improve PI-induced fetal growth restriction in mice [32]. Furthermore, fetal growth restriction predisposes to spontaneous preterm delivery and is in some cases a medical indication to induce a preterm delivery [70]. Further studies should be conducted to explore whether progesterone supplementation reduces the risk of SGA/fetal growth restriction, in relation to PI-based cART, placental dysfunction and progesterone level.

The most common cART regimens differed between included studies that compared timing of initiation. In six of these studies, the proportion of women on PI-based cART was more than 50% of the total sample size for the SGA analyses, whereas the proportion was below 10% in all other studies included in the main meta-analysis. In studies where the majority of women were not on PI-based cART and cART drugs were known, nevirapine- or efavirenz-based cART (NNRTI-based) were the most commonly used cART regimens. The different sensitivity analyses performed did not indicate any substantial variation in the risk of SGA between different cART regimens; however, this should be further explored.

Although the benefits of cART largely outweigh the risks, the current study findings indicate a tendency towards slightly higher risks of having an SGA infant. Exposure to PI-based cART or cART initiated before pregnancy might be reasonable to include in a history-based risk stratification for fetal growth restriction during early pregnancy. Women at high risk for fetal growth restriction should undergo close surveillance of fetal growth, which could include serial ultrasound measurement of fetal size and assessment of wellbeing with umbilical artery Doppler [30,34]. Detection of fetal growth restriction may lead to changes in the timing and mode of delivery. Also, treatment with aspirin should be considered in a pregnancy with high risk of fetal growth restriction for women with a history of placenta-mediated fetal growth restriction or risk of pre-eclampsia.

There are several limitations to this systematic review. Women on cART before conception might historically represent a group of individuals that are more susceptible to adverse outcomes for other reasons, such as more severe HIV disease. Hence, this could represent a risk of confounding by indication. CD4 cell count is a common measure of HIV disease severity. Among the included studies that investigated an association between CD4 cell count and SGA, all except one found no association. In addition, not all included studies adjusted for CD4 cell count. Treatment guidelines have changed the eligibility criteria based on CD4 cell count, thus HIV disease severity in the included study populations can be assumed to differ depending on when the study was conducted. The adjustment variables in multivariable analyses also differed between the included studies. Furthermore, the way SGA was measured was not uniform across the included studies. Some studies based their data on gestational weeks on ultrasound, whereas others based these measurements entirely on physical examination and last menstrual period, which provide less accurate estimates of gestational age compared with ultrasound [71]. SGA in the newborn is also an imperfect proxy for fetal growth restriction, and it is difficult to differentiate between newborns who are small due to fetal growth restriction and those who are constitutionally small but healthy newborns [30]. However, neither biochemical- nor ultrasound-based markers are recommended for universal screening of fetal growth restriction. A reasonable approach, particularly in resource-limited settings, might be to assess the risk for SGA during early pregnancy, including the risk factors studied in this review and several others. Additionally, the GRADE evaluation highlighted several biases in the reviewed papers. The observational study design set the grade of evidence initially to low. Other measures further reduced the grade of evidence, particularly for the meta-analysis comparing PI-based cART with non-PI-based cART. The substantial heterogeneity between the reported effect estimates might be due to differences in type of cART drugs, dosages, or specific time of initiation. The heterogeneity might have been even greater if the main meta-analyses had not been restricted to studies with >80% of the reference group on NNRTI-based cART for the first research question and >80% of the whole study sample on NNRTI-based cART for the second research question. Both the low and very low grade of evidence imply that future research may change the conclusions drawn herein. Lastly, most of the studies that compared the timing of cART initiation did not take into account the exact time of initiation, how long time the woman had been exposed to cART before conception, or in which gestational week cART was initiated after conception.

One key strength of this systematic review is that two authors independently performed the screening and extraction process. Also, the systematic review and meta-analysis were conducted in accordance with the updated PRISMA guidelines, a variety of databases and grey literature were searched, and broad search terms were used.

## 5. Conclusion

The results of this systematic review and meta-analysis indicated that both PI-based cART and initiation of cART before conception may slightly increase the risk of having an SGA infant compared with cART without a PI and initiation of cART after conception, respectively. This indicates that careful monitoring of fetuses exposed to PI-based cART or cART before pregnancy might be reasonable. Based on the uncertainty of evidence, further research may change this conclusion.

## Contributors

TR, with continuous input and supervision from IFS, conceived the study proposal, did the literature search and the statistical analyses, wrote the drafts, and assessed the certainty of evidence. TR and IFS independently screened the titles and abstracts, and extracted the data. TR, IFS, RTL and AKD developed the approach and design for the systematic review and meta-analysis. IFS had overall supervision of the process. RTL contributed to the statistical analyses. All authors contributed to, commented on, and approved the final manuscript, and all had full access to all the data in the study and accepted the responsibility to submit for publication.

## Declarations

**Funding:** The University of Bergen funded a PhD position for the corresponding author TR.

**Competing Interests:** We declare no competing interests.

**Ethical Approval:** Not required.

**Sequence Information**: Not applicable.

## Data sharing

All details on the search strategy, drug details, and inclusion criteria in the different analyses can be found in the Supplementary Materials.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2023.106823.

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