

Title

Systematic review and meta-analysis of perinatal outcomes associated with maternal HIV-infection.

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Summary

Background

The HIV pandemic affects 35 million people globally, with 91% of HIV-positive pregnant women residing in sub-Saharan Africa, a region that also has very poor perinatal outcomes. We aimed to establish whether maternal HIV-infection is associated with specific perinatal outcomes.

Methods

We undertook a systematic review and meta-analysis to determine the association between antiretroviral (ART)-naïve maternal HIV-infection and 11 perinatal outcomes: preterm birth (PTB), very PTB (VPBT), low birthweight (LBW), very LBW (VLBW), term-LBW, preterm-LBW, small-for-gestational-age (SGA), very SGA (VSGA), miscarriage (MC), stillbirth (SB) and neonatal death (NND). We systematically searched PUBMED, CINAHL, Global Health, EMBASE, the Cochrane Central database, WHO clinical trials database, Pan African Trials database, ClinicalTrials.gov database, and ISRCTN register for studies published from 1 January 1980 to 7 December 2014. We included prospective and retrospective cohort studies and case-control studies reporting on perinatal outcomes in ART-naïve HIV-positive women and HIV-negative controls. Meta-analyses using a random-effects model were performed for specific perinatal outcomes. Subgroup and sensitivity analyses were conducted and correction for confounders assessed.

Findings

Twenty prospective and 12 retrospective cohort studies, and three case-control studies, including 53,623 women, were included in the analysis. Meta-analyses of prospective cohort studies show that maternal HIV-infection is associated with an increased risk of PTB (RR 1.50; 95%CI 1.24-1.82), LBW (RR 1.62; 95%CI 1.41-1.86), SGA (RR 1.31; 95%CI 1.14-1.51) and SB (RR 1.67; 95%CI 1.05-2.66). Retrospective cohort studies also indicate an increased risk of term-LBW (RR 2.62; 95%CI 1.15-5.93) and preterm-LBW (RR 3.25; 95%CI 2.12-4.99). The strongest and most consistent evidence for these associations is found in sub-Saharan Africa. No association was found between maternal HIV-infection and VPTB, VSGA, VLBW, MC, or NND, though the evidence relating to these outcomes was limited. Correction for confounders did not affect the significance of these findings.

Interpretation

ART-naïve maternal HIV-infection is associated with PTB, LBW, SGA and SB, especially in sub-Saharan Africa. There is an urgent need to assess how ART regimens affect these perinatal outcomes.

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Introduction

Maternal HIV infection, with its associated maternal morbidity and mortality and risk of mother-to-child transmission of HIV, impacts three Millennium Development Goals (MDGs): reducing child mortality (MDG 4), improving maternal health (MDG 5), and combating HIV/AIDS and other diseases (MDG 6).¹ The disease burden caused by HIV-infection is reduced by antiretroviral therapy (ART), but coverage is incomplete.² Consequently, the MDG targets will not be met by 2015 and high rates of maternal and child mortality and morbidity will persist, particularly in sub-Saharan Africa where 91% of HIV-infected pregnant women live.¹⁻³

It is unclear whether maternal HIV-infection affects perinatal outcomes, which are major contributors to poor health globally. Annually, there are an estimated 2.6 million stillbirths (SB),⁴ 2.8 million neonatal deaths (NND),⁵ 14.9 million preterm births (PTB),⁶ 32.4 million small-for-gestational-age (SGA) infants,⁷ and 18 million low birthweight (LBW) infants.⁷ These outcomes are inter-related, with PTB being the leading cause of neonatal and child mortality,^{5,8} fetal growth restriction being associated with SB,⁹ and 41% of LBW infants being preterm.⁷ Sub-Saharan Africa has the highest rates of SB and NND worldwide,^{4,10} and nine of the 11 countries with the highest PTB rates are also in sub-Saharan Africa,⁶ which has the second highest SGA and LBW rates after South Asia.⁷ Therefore, sub-Saharan Africa carries very high adverse perinatal outcome rates as well as the highest burden of maternal HIV-infection.

We aimed to establish whether maternal HIV infection is associated with specific perinatal outcomes. To this end we undertook a systematic review and meta-analysis

to determine the association between ART-naïve maternal HIV-infection and 11 perinatal outcomes.

Methods

Literature search strategy

The Cochrane review guidelines were used to develop a systematic review protocol,¹¹ which was registered online prior to conducting the review (PROSPERO: CRD42013005637). 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) were searched to identify studies published between 1 January 1980 and 7 December 2014. In an effort to ensure that all relevant studies were identified, two search strategies were developed and adapted for each database (appendices 1 and 2). The search terms used covered “HIV”, “ART”, “pregnancy outcome”, “preterm birth”, “intrauterine growth restriction”, “low birthweight”, and “stillbirth”. No methodological or language filters were applied. Studies from all countries were eligible. Full text articles and abstracts were considered. The references of studies included in this review, and a review published in 1998,¹² were assessed for additional citations. Authors were contacted when the full text manuscript contained insufficient information.¹³

Study selection and data-extraction

Two authors independently reviewed the citations retrieved by the literature search and identified relevant citations. Full text manuscripts were obtained and screened by one reviewer using the following eligibility criteria:

- Population: Pregnant women with known perinatal outcomes.

- Exposure: HIV-infection, contracted before or during pregnancy, irrespective of the route of transmission. Women should not have been exposed to ART during pregnancy, with the exception of a single dose at delivery.
- Comparison: HIV-negative pregnant women from the same community as the HIV-positive participants.
- Outcomes: 11 perinatal outcomes, in four categories, were assessed:
 1. Gestational age at delivery: PTB ($<37^{+0}$ weeks' gestation);⁶ very PTB (VPTB, $<32^{+0}$ weeks' gestation).⁶
 2. Birthweight (BW): LBW (BW <2500 g);⁷ very LBW (VLBW, BW <1500 g).⁷
 3. Birthweight and gestational age at delivery: Term-LBW ($\geq 37^{+0}$ weeks' gestation and BW <2500 g);⁷ preterm-LBW ($<37^{+0}$ weeks' gestation and BW <2500 g); SGA (BW for gestational age $<10^{\text{th}}$ centile);¹⁵ very SGA (VSGA, BW for gestational age $<3^{\text{rd}}$ centile).¹⁵
 4. Fetal and neonatal mortality: Miscarriage (MC, spontaneous expulsion of fetus $<24^{+0}$ weeks gestation);¹⁶ SB (any 3rd trimester delivery of stillborn infant with BW ≥ 1000 g⁹ or $\geq 24^{+0}$ completed weeks¹⁷ or ≥ 35 cm body length⁹); NND (death of an infant within the first 28 days of life).¹⁸

Outcomes were not extracted if they were not defined or the study definition differed to that specified in our protocol. Data regarding preterm prelabour rupture of membranes (PPROM) were also sought, but no papers reporting this outcome were found.

- Study design: Randomised controlled trials (RCT), prospective and retrospective cohorts, case-control and cross-sectional studies.

Ambiguities about study eligibility were resolved by discussion (a list of excluded studies is available upon request). Two authors independently assessed the uniqueness

of each study population. If the same cohort was reported more than once, the manuscript with the most recent and complete data was retained; however, manuscripts reporting different outcomes for the same cohort were both included.^{19,20} Perinatal outcome data were extracted (table 1), plus reported unadjusted and adjusted relative risks (RR) and odds ratios (OR), and 95% confidence intervals (CI), to assess the effect of adjusting for confounders. Any disagreements were resolved by discussion among the authors.

Methodological quality

Two authors independently assessed the methodological quality of each study using a modified Newcastle-Ottawa Scale.²¹ Cohort studies were assessed according to nine criteria in three groups: (1) Selection of HIV-positive and negative participants (maximum 4 points), (2) Comparability of exposed and unexposed participants, and whether corrections were made for confounding factors (maximum 2 points), and (3) Methods to assess the outcome of interest, including method used to estimate gestational age at delivery (maximum 3 points) (appendix 3). A similar grading system was used for case-control studies with minor alterations to accommodate the study design (appendix 4). The definitions of good, average and poor quality appear in appendix 5.

Data synthesis

Dichotomous outcome data extracted from individual studies were used to generate a RR (cohort studies) or OR (case-control studies), irrespective of study quality. A meta-analysis was conducted when two or more studies with the same study design reported on the same outcome. A random-effects model was used to calculate a

weighted summary effect estimate and 95%CI for the association between maternal HIV-infection and individual perinatal outcomes.¹¹ Thereafter, the summary effect estimates and 95%CI for individual outcomes, according to study design, were represented on a forest plot. Within each meta-analysis, the I^2 statistic was used to determine the proportion of heterogeneity in the effect estimate attributable to clinical or methodological variability, as opposed to sampling error.¹¹ The degree of heterogeneity was interpreted as none (<25%), low (25-49%), moderate (50-74%), and high ($\geq 75\%$).¹¹

Pre-specified subgroup analyses were conducted to explore the influence of covariates on the association between maternal HIV-infection and outcomes,¹¹ including geographical location where the study was performed and the method used to determine gestational age.

Sensitivity analyses were conducted to explore whether methodological quality and the adjustment for confounding factors influenced the observed associations between maternal HIV-infection and outcomes.¹¹ The Peters' test was used to assess publication bias in meta-analyses containing a minimum of 10 studies.²² All statistical analyses were conducted using STATA version 13 (College Station, TX, USA), and the systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²³

Results

Characteristics of included studies

The search strategy yielded 60,750 citations, 35 of which were included (figure 1), involving 53,623 women in 20 prospective and 12 retrospective cohorts studies, and three case-control studies.^{13,19,20,24–55} No RCTs were found. The study and population characteristics, methods used to correct for confounders, gestational age estimation methods, and quality assessment ratings are displayed in table 1.

Of the 35 studies, 25 (71%) were conducted in sub-Saharan Africa (table 1). The most commonly reported perinatal outcomes were LBW (26 studies), PTB (24 studies), SGA (7 studies), and term-LBW (7 studies). The remaining outcomes were each reported in fewer than 5 studies (figure 1, table 1).

Two-thirds [24 (69%)] of included studies reported on how gestational age was estimated (table 1). Half of these used a single method: late ultrasound (≥ 14 weeks' gestation; 3 studies), last normal menstrual period (4 studies), or neonatal assessment (5 studies); the other half used mixed-methods (appendix 7). No study used a first trimester ultrasound scan, the most accurate method to determine gestational age. As a result, there were no good quality studies, 20 (57%) were average and 15 (43%) poor quality (table 1, appendix 8).

In the majority of studies, antenatal ART were not provided because the studies were conducted before 1994, when ART had not yet been demonstrated to be effective in the prevention of mother-to-child transmission of HIV and was therefore not yet in clinical practice [21 studies (60%)] (table 1).⁵⁶ In other studies, ART was not yet recommended in national treatment guidelines (1 study),⁴⁹ recommended but not available (2 studies)^{19,31}, only intrapartum ART were provided (2 studies)^{20,44} and in

two case-control studies HIV was diagnosed postpartum, thereby precluding ART use.^{40,45} In the remaining 7 studies no reason was specified.

Association of maternal HIV-infection with gestational age at delivery

Preterm birth (34,337 women studied)

Maternal HIV-infection was significantly associated with PTB in the meta-analysis of 14 prospective (RR 1.50; 95%CI 1.24-1.82) and eight retrospective (RR 1.82; 95%CI 1.41-2.34) cohort studies (figure 2). The association was significant in both sets of studies in sub-Saharan Africa and the Americas & Caribbean (figure 3A,B). Among prospective cohort studies where method of gestational age assessment was specified, the type of method of gestational age assessment did not alter the significant association between maternal HIV-infection and PTB (appendix 10A). Sensitivity analysis according to methodological quality showed a significant association in both average (RR 1.64; 95%CI 1.23-2.20) and poor quality prospective studies (RR 1.34; 95% CI 1.06-1.71) (appendix 11A). Retrospective studies were heterogeneous ($I^2 = 81.0\%$) (appendix 13.1). Seven studies reported both unadjusted and adjusted effect estimates for PTB (figures 4A,B). In all cases the adjustment for covariates had no effect on the direction or significance level of the effect estimates. The Peters' test showed no evidence of publication bias ($P = 0.660$). One prospective cohort study reported an increased risk of PTB with more advanced HIV disease (appendix 12).²⁹ Two case-control studies showed no significant association with PTB (appendix 9).

^{40,45}

Very preterm birth (2,368 women studied)

One prospective cohort study reported no association between maternal HIV-infection and VPTB (RR 0.99; 95%CI 0.60-1.65) (figure 2).¹⁹

Association of maternal HIV-infection with birthweight

Low birthweight (36,312 women studied)

Maternal HIV-infection was significantly associated with LBW in the meta-analysis of 16 prospective (RR 1.62; 95%CI 1.41-1.86) and nine retrospective (RR 1.93; 95%CI 1.48-2.52) cohort studies (figure 2). The association was significant in both sets of studies in sub-Saharan Africa and Asia (figure 3A,B), irrespective of study quality (appendix 11A,B). Heterogeneity was observed among retrospective studies ($I^2 = 87.2\%$) (appendix 13.12). Adjustment for covariates had no effect on the direction or significance level of the effect estimates (figure 4A,B). Two prospective cohort studies reported an increasing risk of LBW with an advancing stage of HIV disease (appendix 12).^{29,41} A small case-control study showed no association with LBW (appendix 9).²⁶

Very low birth weight (58 women studied)

One small retrospective cohort study reported a positive, but non-significant association between maternal HIV-infection and VLBW (RR 4.82; 95%CI 0.47-49.72) (figure 2).⁵²

Association of maternal HIV-infection with birthweight and gestational age at delivery

Term-LBW (7,038 women studied)

Maternal HIV-infection was significantly associated with term-LBW in the meta-analysis of two retrospective cohort studies (RR 2.62; 95%CI 1.15-5.93) (figure 2),^{29,36} irrespective of geographical region, gestational age assessment method or study quality (figure 3, appendices 10 and 11), and after adjusting for confounders in the

single study which assessed this (figure 4B).⁵¹ This, however, was in the presence of a high degree of between-study heterogeneity ($I^2 = 89.8\%$) (appendix 13.23). The association in the meta-analysis of five prospective cohort studies did not reach significance (RR 1.30; 95%CI 0.98-1.72). No effect of HIV disease stage on the rate of term-LBW was seen in the one study which examined this (appendix 12).²⁹

Preterm-LBW (2,199 women studied)

Maternal HIV-infection was significantly associated with preterm-LBW in one retrospective cohort study (RR 3.25; 95%CI 2.12-4.99) (figure 2),⁴³ which was conducted in sub-Saharan Africa, used mixed-methods for gestational age assessment, and was of low quality (figure 3B, appendices 10B and 11B). The association in the meta-analysis of two prospective cohort studies was not significant (RR 1.18; 95%CI 0.91-1.54).^{29,36} One prospective cohort study reported an increased risk of preterm-LBW with more advanced HIV disease (appendix 12).²⁹

Small-for-gestational-age (14,315 women studied)

Maternal HIV-infection was significantly associated with SGA in the meta-analysis of four prospective (RR 1.31; 95%CI 1.14-1.51) and three retrospective (RR 2.08; 95%CI 1.26-3.46) cohort studies (figure 2). The association was significant in both sets of studies in sub-Saharan Africa (figure 3), irrespective of gestational age assessment method and study quality, except for one poor quality prospective study (appendices 10 and 11).¹⁹ Heterogeneity was observed in the meta-analysis of retrospective studies ($I^2 = 85.2\%$) (appendix 13.37). Among the studies that assessed confounding, the effect estimates remained significant after adjustment for covariates in three studies (figure 4A,B), in one study¹⁹ the multivariate analysis allowed the effect estimate to reach statistical significance, and in another study²⁵ the estimate lost significance (figure 4A,B).

Very small-for-gestational-age (2,368 women studied)

One prospective study in sub-Saharan Africa reported a positive, but non-significant, association between maternal HIV infection and VSGA (RR 1.28; 95%CI 0.95-1.71) (figure 2).¹⁹ Adjustment for covariates did not alter the effect estimate (figure 4A).

Association of maternal HIV-infection with fetal and neonatal mortality

Miscarriage (125 women studied)

One prospective cohort study in the Americas found no association between maternal HIV infection and MC (RR 1.40; 95%CI 0.37-5.36) (figure 2).⁵³

Stillbirth (1,168 women studied)

The meta-analysis of two prospective cohort studies in sub-Saharan Africa found a significant association of maternal HIV infection with SB (RR 1.67; 95%CI 1.05-2.66) (figure 2).^{28,33} Only the average quality study using mixed-methods for gestational age assessment showed a significant association (appendices 10A and 11A).²⁸

Neonatal death (2,667 women studied).

The meta-analysis of three prospective cohort studies in sub-Saharan Africa showed a positive but non-significant association of maternal HIV infection with NND (RR 1.68; 95%CI 0.45-6.29), in the presence of substantial heterogeneity ($I^2 = 89.9$) (appendix 13.56). One retrospective cohort study also found no association with NND (RR 2.00; 95%CI 0.61-6.54) (figure 2).³⁵

Discussion

This systematic review collates the evidence regarding the effect of ART-naïve maternal HIV infection on perinatal outcomes at a stage in the epidemic when an increasing number of pregnant women globally are receiving ART, making the likelihood of new evidence emerging in the future low. We found that HIV-infection is strongly associated with increased risks of PTB, LBW, SGA and SB, and weakly with term-LBW and preterm-LBW (figure 2). While only two studies reported on specific perinatal outcomes according to HIV disease stage,^{29,41} the risk of adverse perinatal outcomes increased with a more advanced stage of disease (appendix 12). No association was observed between the place of delivery and perinatal outcomes (table 1 and data not shown). The evidence did not support an effect on VPTB, VLBW, VSGA, MC, or NND (figure 2). Overall, the evidence is strongest and most consistent in sub-Saharan Africa, the region carrying the highest burden of maternal HIV-infection, and largely persists irrespective of the study quality, method of gestational age determination and controlling for confounding factors.

Our review has numerous strengths. Firstly, a systematic review and meta-analysis of observational studies generates the best possible evidence to evaluate the effect of ART-naïve maternal HIV-infection on perinatal outcomes. The literature search included all study designs and no language or geographical restrictions. We clearly defined the outcomes of interest *a priori* and strictly applied the eligibility criteria to reduce misclassification bias. Two independent reviewers applied the eligibility criteria and methodological assessments, and extracted the data. We used a random-effects model, which accounts for heterogeneity, and conducted numerous subgroup and sensitivity analyses to explore unexplained heterogeneity, as well as the presence

and effect of underlying or residual bias and confounding. We assessed the effect of adjustment for confounding factors in individual studies. When applicable, the Peters' test confirmed an absence of publication bias and the systematic review was reported according to the PRISMA guidelines.²³ As 91% of HIV-infected pregnant women reside in sub-Saharan Africa and most of the primary data in our review originated from that region, our findings are particularly relevant to those countries with the highest burden of maternal HIV infection.

A similar previous review only included publications up to 1996, many of which were abstracts.¹² Furthermore, this previous review used a fixed-effects model to pool the data despite the substantial between-study heterogeneity; it also included fewer outcomes, which were poorly or not defined, and gestational age estimation methods were not assessed. In contrast, our systematic review and meta-analysis are based on up-to-date data (publications in 1989-2014), well-defined outcomes, and advanced methodologies.

Our review has some limitations. Certain perinatal outcomes were only reported by a small number of studies, which precluded drawing firm conclusions. While including studies that did not define outcomes, or defined outcomes differently to our protocol, could have increased the power of our analyses, it would have compromised the review's validity by introducing bias. Secondly, due to the limited reporting of unadjusted and adjusted effect estimates, only six outcomes were assessed in this sensitivity analysis. Furthermore, studies adjusted for a variety of covariates and therefore a pooled analysis of adjusted estimates could not be conducted.¹¹ Residual confounding cannot be excluded. We could not assess the influence of certain important confounders (e.g. maternal viral load and CD4⁺ count), which are associated with adverse outcomes, because of limited measurement, adjustment and

reporting of these confounders in included studies. Furthermore, many studies failed to mention how gestational age was determined, and none used an ultrasound scan <14 weeks of gestation, the most accurate method of gestational age estimation,⁵⁷ which may have contributed to misclassification bias and some of the heterogeneity observed, as most of the outcomes depend on accurate estimation of gestational age. No distinction was made between spontaneous and caregiver-initiated PTB. The methods and accuracy of birthweight measurements were not specifically assessed in our review. Finally, SGA and VSGA cut-offs were based on a variety of centile charts rather than international standards.¹⁵ Similar challenges are encountered in many other studies assessing perinatal outcomes in low and middle-income countries,⁵⁸ which emphasizes the importance of using accurate and consistent methods of gestational age estimation⁵⁷ and international standards in future studies.¹⁵

Our study indicates that maternal HIV infection differentially affects individual perinatal outcomes. The effect of maternal HIV infection on PTB, LBW, SGA and SB is clear, with significantly increased risks in both prospective and retrospective cohort studies. However, the effects on PTB, LBW and SGA did not translate into an effect on NND, for which the data were highly heterogeneous. The evidence is weaker for term-LBW and preterm-LBW, where an effect of HIV infection was seen in retrospective, but not prospective cohort studies. VPTB, VSGA, and VLBW are associated with greater morbidity and mortality than PTB, SGA, and LBW, respectively, but are less common and also less often reported, with only one study reporting on each of these outcomes. One prospective study with 2368 participants reported no effect of maternal HIV infection on VPTB and VSGA, and the retrospective study reporting on VLBW had only 58 participants. MC was only reported by one prospective study with 125 participants. The limited evidence

available for VPTB, VSGA, VLBW, NND and MC therefore prevents a definitive conclusion regarding an effect of maternal HIV infection on these outcomes.

How HIV-infection results in these specific outcomes is uncertain. The pathogenesis of PTB, SGA, SB, and NND is complex and the underlying causes and clinical presentations very diverse. Indeed, often no cause is identified.^{5,9,14} For example, preterm birth is a heterogeneous syndrome associated with a wide range of clinical phenotypes, which may be maternal, fetal or placental in origin, that are associated with distinct prognoses.¹⁴ Maternal HIV-infection induces a chronic state of inflammation and immune activation, which may interfere with the normal immunological processes of pregnancy maintenance.^{59,60} Some have postulated that HIV has a direct effect on placental growth and function;⁶¹ while others suggest that the effects may be due to intrauterine HIV-infection of the infant.⁶² Only a small proportion of mother-to-child transmission of HIV occurs before 36 weeks, which makes a role of *in-utero* HIV infection in pathogenesis less likely.⁶³ We did not assess whether HIV transmission itself was associated with perinatal outcomes in our study. Finally, some have attributed adverse perinatal outcomes to poor general maternal health caused by HIV infection.²⁹ However, not all perinatal outcomes are affected equally by maternal HIV-infection and while the use of ART in pregnancy improves maternal health,² it appears to increase rates of at least some perinatal outcomes.^{64,65} Future research efforts need to be directed towards the understanding of the biological mechanisms underlying adverse perinatal outcomes in the context of HIV-infection. The increases in PTB, SGA, LBW and SB seen in maternal HIV infection indicate that maternal HIV infection is a major contributor to the global burden of perinatal and child morbidity and mortality. The fact that 91% of HIV-positive pregnant women live in sub-Saharan Africa means that the effects on the burden of disease are

most pronounced in this region. In 2013, 32% of HIV-infected pregnant women in Africa did not receive any ART in pregnancy⁶⁶ and were therefore exposed to a higher risk of PTB, LBW, SGA and SB. New WHO guidance recommends that all pregnant women receive triple ART, and zidovudine (AZT) monotherapy is no longer recommended.⁶⁷ While both treatment options have similar efficacy in preventing mother-to-child transmission of HIV, triple therapy provides additional maternal health benefits.⁶⁷ However, the impact of different ART regimens on perinatal outcomes is uncertain. Accumulating evidence suggests that triple therapy, as compared to AZT monotherapy or dual therapy, is associated with increased rates of adverse outcomes, including PTB, SGA, LBW and SB.^{64,65,68} The maternal and transmission-prevention benefits of triple ART may therefore need to be balanced against an increase in adverse perinatal outcomes. An urgent need therefore exists to assess the effects of different antenatal ART regimens on perinatal outcomes as well as all-cause neonatal and child morbidity and mortality.

Research in Context panel

Evidence before this study

A systematic review and meta-analysis on perinatal outcomes associated with maternal HIV infection was published in 1998. Only publications up to 1996 were included, many of which were abstracts. The perinatal outcomes were poorly or not defined, gestational age estimation methods were not assessed, and a fixed-effects model was used to pool the data despite substantial between-study heterogeneity.

Added value of this study

We have conducted a systematic review and meta-analysis including studies published up to 2014, at a stage in the epidemic when an increasing number of pregnant women globally are receiving antiretroviral therapy (ART), making the likelihood of new evidence emerging in the future low. Perinatal outcomes were clearly defined *a priori*, inclusion and exclusion criteria were strictly applied to reduce bias, and a random-effects model was used to pool the data. Our study shows that ART-naïve maternal HIV-infection is strongly associated with increased risks of preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA) and stillbirth, and weakly associated with term-LBW and preterm-LBW. The evidence did not support an effect on very PTB, very LBW, very SGA, miscarriage, or neonatal death.

Implications of all the available evidence

The evidence for an association of maternal HIV infection with adverse perinatal outcomes is strongest and most consistent in sub-Saharan Africa, the region carrying

the highest burden of maternal HIV-infection. ART reduces maternal morbidity and mortality and greatly reduces mother-to-child transmission of HIV, but the impact of different ART regimens on perinatal outcomes is uncertain. The World Health Organisation recommends triple-drug ART regimens during pregnancy for all HIV-infected women and to continue lifelong treatment when ART is initiated in pregnancy. With continued expansion of treatment programmes, especially in sub-Saharan Africa, an urgent need exists to assess the impact of antenatal ART regimens on perinatal outcomes.

Contributors

COOW wrote the systematic review protocol, assisted with the literature search, screened the search results for relevant manuscripts and assessed their eligibility for the review, conducted methodological quality assessment, extracted data, conducted the meta-analysis, sensitivity analyses, and subgroup analyses, interpreted the data and wrote the first draft of the manuscript.

SK is a qualified librarian and designed and conducted the literature search, and contributed to earlier drafts of the manuscript.

SH provided statistical support and contributed to earlier drafts of the manuscript.

RC assisted with screening of the search results for relevant manuscripts.

SHK contributed to the coordination of the study, the assessment of eligibility, methodological quality, and extracted data, interpreted the data, and co-wrote the manuscript.

JH conceived, designed and coordinated the study, co-wrote the systematic review protocol, assisted with the literature search, the assessment of eligibility, methodological quality, and extracted data, interpreted the data, and co-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.

Conflicts of interest

We declare that we have no conflicts of interest.

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Legends

Table 1. Characteristics of studies included in the systematic review.

AIDS = Acquired Immunodeficiency Syndrome, ART = Antiretroviral therapy, CDC = Centers for Disease Control and Prevention, HIV = Human Immunodeficiency Virus, LBW = low birthweight, LNMP = last normal menstrual period, MC = miscarriage, NND = neonatal death, PTB = preterm birth, SB = stillbirth, SES = socio-economic status, SFH = symphysio-fundal height, SGA = small-for-gestational-age, VLBW = very low birthweight, VPTB = very preterm birth, VSGA = very small-for-gestational-age, WHO = World Health Organisation.

* Studies designated as a case-control study by authors but found to be cohort studies and analyzed as such for the purpose of this systematic review.

§ The confounding factors corrected for in each study are detailed in appendix 6

Figure 1. Schematic representation of study selection process.

PTB = preterm birth, VPTB = very preterm birth, LBW = low birthweight, VLBW = very low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age, MC = miscarriage, SB = stillbirth, NND = neonatal death. See Methods for definitions of perinatal outcomes. “Inappropriate population” e.g. HIV-positive women who are not pregnant, “Not relevant to review” e.g. Assisted Reproductive Technology (ART), “Insufficient data” e.g. perinatal outcomes not reported according to HIV-status of women.

Figure 2. Perinatal outcomes associated with ART-naïve maternal HIV infection, by study design.

Summary forest plot displaying the random-effects meta-analysis results of the association between ART-naïve maternal HIV-infection and perinatal outcomes in prospective and retrospective cohort studies. Statistically significant effects are presented in red. RR (95%CI) = relative risk with 95% confidence interval, n = number, % = number of HIV-positive participants as a proportion of the total number of participants in the included studies (for each outcome and study design). PTB = preterm birth, VPTB = very preterm birth, LBW = low birthweight, VLBW = very low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age, MC = miscarriage, SB = stillbirth, NND = neonatal death. See Methods for definitions of perinatal outcomes.

Figure 3. Perinatal outcomes associated with ART-naïve maternal HIV infection, by geographic region. A: Prospective cohort studies, B: Retrospective cohort studies.

Summary forest plots displaying the random-effects meta-analysis results of the association between ART-naïve maternal HIV-infection and perinatal outcomes, stratified according to the geographic region where studies were conducted. Statistically significant effects are presented in red. RR (95%CI) = relative risk with 95% confidence interval, n = number, % = number of HIV-positive participants as a proportion of the total number of participants in the included studies (for each outcome and study design). PTB = preterm birth, VPTB = very preterm birth, LBW = low birthweight, VLBW = very low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age, MC = miscarriage, SB = stillbirth, NND = neonatal death. See Methods for definitions of perinatal outcomes.

Figure 4. Sensitivity analysis of the adjustment for confounding factors in studies that assessed the association between ART-naïve maternal HIV-infection and perinatal outcomes. A: relative risk (RR) estimates, B: odds ratio (OR) estimates.

A. Sensitivity analysis displaying the reported unadjusted relative risk (RR) and adjusted relative risk (ARR) for the association between ART-naïve maternal HIV-infection and perinatal outcomes. For all analyses ARR 1 = multivariate analysis. For Coley et al. (2001) ARR 2 = Age-adjusted RR. For Leroy et al (1998) ARR 2 = Mantel-Haenzel estimate adjusting for prematurity. RR (95%CI) = relative risk with 95% confidence interval. **B:** Sensitivity analysis displaying the reported unadjusted odds ratio (OR) and adjusted odds ratio (AOR) for the association between ART-naïve maternal HIV-infection and perinatal outcomes. For all analyses AOR 1 = multivariate analysis, except for Ayisi et al (2003) where AOR 1 = multivariate analysis in primigravidae, and AOR 2 = multivariate analysis in multigravidae. OR (95%CI) = odds ratio with 95% confidence interval.

Adjusted effect estimates are presented in orange. Studies are listed in alphabetical order of first author within each category. Covariate factors adjusted for in graphs A and B are detailed in appendix 6 (Regression analysis - Multivariable analysis). PTB = preterm birth, LBW = low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age. See Methods for definitions of perinatal outcomes.

Table 1: Characteristics of studies included in the systematic review.											
Study	Country	Study design	Recruitment time period	Number of pregnant women included in analysis (n)		Perinatal outcomes	Population characteristics	HIV disease stage and reason why antenatal ART not provided	Methods to correct for confounding factors §	Gestational age estimation method	Quality Assessment
				HIV-positive	HIV-negative						
Sub-Saharan Africa											
Adjorlolo et al 1991 ²⁴	Ivory Coast	Retrospective cohort	Not reported	290	2768	LBW	Low SES, largest urban area in the country.	4-15% of women met criteria for AIDS. ART not yet demonstrated to be effective in pregnancy.	None	Unspecified	Poor
Ayisi et al 2003 ²⁵	Kenya	Prospective cohort	June 1996-March 1999	420	1503	PTB, LBW, SGA	Uncomplicated singleton pregnancies without comorbidities. Urban setting. All women delivered in hospital.	No description on HIV disease stage or why ART not provided.	Regression analysis	Neonatal assessment (Dubowitz)	Average
Bergstrom et al 1995 ²⁶	Mozambique	Case-control	Not reported	51 cases	51 controls	LBW	No description.	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	Matching	Unspecified	Average
Braddick et al 1990 ^{27*}	Kenya	Prospective cohort	January 1986-March 1989	177	326	PTB, LBW	Lower SES, urban setting, no history of intravenous drug use. All women delivered in hospital.	55% of women were asymptomatic, 45% were symptomatic, one woman had AIDS. ART not yet demonstrated to be effective in pregnancy.	Risk factor analysis	Neonatal assessment (Ballard) and LNMP	Average
Bulterys et al 1994 ²⁸	Rwanda	Prospective cohort	October 1989-February 1992	308	299	PTB, LBW, SGA, SB, NND	Semirural setting where 75% of deliveries occurred at home.	Majority of HIV-positive women were asymptomatic and none met the criteria for AIDS. ART not yet demonstrated to be	Risk factor analysis, regression analysis	Neonatal assessment (Ballard) and late ultrasound	Average

								effective in pregnancy.			
Coley et al 2001 ²⁹	Tanzania	Prospective cohort	April 1995-July 1997	522	485	PTB, LBW, Term-LBW, Preterm-LBW	Cohort representative of the general population. 93.5% of deliveries occurred at medical facility, 3.6% at home and 2.9% at non-medical facility.	83% of women were asymptomatic (WHO stage 1), 17% were symptomatic (WHO ≥ 2). No description on why ART not provided.	Risk factor analysis, regression analysis	Unspecified	Average
Ezeaka et al 2009 ³⁰	Nigeria	Prospective cohort	August 2002-August 2005	220	218	PTB, LBW	Participants recruited in a tertiary hospital in urban setting. None of the women reported use of intravenous drugs, alcohol or tobacco. All women delivered in hospital.	85.5% of women were asymptomatic and 14.5% met WHO criteria for AIDS. No description on why ART not provided.	Matching, risk factor analysis	LNMP and late ultrasound	Average
Friis et al 2004 ³¹	Zimbabwe	Prospective cohort	1996-1997	360	725	PTB, LBW, Term-LBW	Low SES, urban setting.	No description on HIV disease stage. ART recommended nationally, but not available.	Regression analysis	LNMP and SFH	Poor
Habib et al 2008 ³²	Tanzania	Retrospective cohort	1999-2006	137	5436	PTB, SGA	Urban and rural settings in 6 districts in Tanzania. Study conducted at a referral hospital and data not representative of the population. All women delivered in hospital.	No description on HIV disease stage or why ART not provided.	Regression analysis	LNMP	Poor
Ladner et al 1998 ³³	Rwanda	Prospective cohort	July 1992-August 1993	275	286	SB	Urban setting. All women delivered in hospital.	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	None	Late ultrasound	Poor
Lallemant et al 1989 ³⁴	Republic of the Congo	Prospective cohort	May 1987-March 1988	61	130	LBW	Urban setting. All women delivered in hospital.	One woman met the WHO criteria for AIDS. ART not yet demonstrated to be effective in pregnancy.	Matching, risk factor analysis	Unspecified	Average

Lepage et al 1991 ³⁵	Rwanda	Retrospective cohort	November 1988-June 1989	215	216	LBW, NND	Urban setting. All women delivered in hospital.	81% were asymptomatic and none met the WHO criteria for AIDS. ART not yet demonstrated to be effective in pregnancy.	Matching, risk factor analysis, regression analysis	Neonatal assessment (Finnström)	Average
Leroy et al 1998 ³⁶	Rwanda	Prospective cohort	July 1992-August 1993	364	365	PTB, LBW, Term-LBW Preterm-LBW	Urban setting. Study sample representative of the population. 12.3% of deliveries occurred at home and 87.7% at a hospital.	92% of women were asymptomatic and one fulfilled the WHO criteria for AIDS. 7.5% of women had a CD4 count < 200 cells/μl. ART not yet demonstrated to be effective in pregnancy.	Matching, risk factor analysis, regression analysis	Neonatal assessment (Finnström) and late ultrasound	Average
Mmiro et al 1993 ³⁷	Uganda	Prospective cohort	December 1988-November 1990	557	697	PTB	Urban setting. No evidence of illicit drug use. 50% of deliveries occurred at home and 50% at a hospital.	46.8% of women were symptomatic. ART not yet demonstrated to be effective in pregnancy.	Risk factor analysis	Unspecified	Poor
Musana et al 2009 ³⁸	Kenya	Prospective cohort	September 2004-April 2005	68	68	PTB, LBW	No description.	All women met the criteria for advanced stage of disease (WHO stage 3 and 4). No description on why ART not provided.	Matching, risk factor analysis	LNMP	Average
Mwanyumba et al 2001 ³⁹	Kenya	Retrospective cohort	May 1996-April 1999	1169	7188	LBW	Singleton pregnancies, no obstetric complications, illicit drug use or smoking. All women delivered in hospital.	No description on HIV disease stage or why ART not provided.	Regression analysis	Unspecified	Poor
Ndirangu et al 2012 ¹⁹	South Africa	Prospective cohort	August 2001-September 2004	1189	1179	PTB, VPTB, SGA, VSGA	Area with a high HIV-prevalence (39.5%). Rural setting, low SES. 11.8% of deliveries occurred at home or on the way to a healthcare facility and 88.2% of deliveries in hospital.	5.5% of HIV-positive women had a CD4 count < 200 cells/μl. ART recommended nationally, but not available.	Risk factor analysis, regression analysis	Neonatal assessment (Ballard) and LNMP	Poor

Noble et al 2005 ⁴⁰	Zimbabwe	Case-control	July 1998-March 1999	53 cases	444 controls	PTB	Urban setting. Convenience sample of pregnant women who delivered term and preterm infants at a university affiliated hospital. All women delivered in hospital.	No description on HIV disease stage. HIV-diagnoses made after delivery, hence no antenatal ART.	Risk factor analysis, regression analysis	Neonatal assessment (Dubowitz), LNMP and SFH	Average
Rollins et al 2007 ²⁰	South Africa	Prospective cohort	September 2001-September 2004	1449	1401	LBW	Low SES, rural, semirural and urban antenatal clinics in an area with a high HIV-prevalence (39.5%). 12.4% of deliveries occurred at home, 28% at a clinic, 52.9% in hospital and 6.5% in an unknown location.	11% of women had a CD4 count < 200cells/μl. Participants received intrapartum ART only.	Regression analysis	Neonatal assessment (Ballard) and LNMP	Average
Ryder et al 1989 ⁴¹	Democratic Republic of the Congo	Prospective cohort	30 April 1986-30 April 1987	466	606	LBW, NND	Urban setting. Recruited from 2 hospitals: hospital A (women of low SES) and hospital B (women of high SES). No illicit drug use.	18% of women met criteria for AIDS. ART not yet demonstrated to be effective in pregnancy.	Matching	Neonatal assessment (Dubowitz)	Average
Sutton et al 1999 ⁴² *	Democratic Republic of the Congo	Retrospective cohort	October 1989-April 1990	215	206	LBW	Urban setting. Singleton pregnancies. All women delivered in hospital.	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	Regression analysis	Neonatal assessment (Ballard) and LNMP	Average
Taha et al 1995 ⁴³	Malawi	Retrospective cohort	October 1989-October 1990	679	687	PTB, LBW, Term-LBW, Preterm-LBW	Urban setting. All women delivered in hospital.	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	None	Neonatal assessment (Ballard) and LNMP	Poor
Temmerman et al 1994 ¹³	Kenya	Prospective cohort	January 1989-December 1991	315	311	PTB, LBW, Term-LBW, NND	Low SES, urban setting, no illicit drug use. 20% of deliveries occurred at home or at another maternity unit.	52.2% of women were asymptomatic, 43.6% were symptomatic and 4.2% met the criteria for AIDS. ART not yet	Matching, risk factor analysis	Late ultrasound	Poor

								demonstrated to be effective in pregnancy.			
Ticconi et al 2003 ⁴⁴	Zimbabwe	Retrospective cohort	1 January-30 June 2000 and 1 January-30 June 2001	52	789	PTB, SGA	Referral hospital in malaria-endemic area. Recruitment only during peak malaria season.	No description on HIV disease stage. Participants received intrapartum ART only.	Regression analysis	LNMP	Poor
Van den Broek et al 2014 ⁴⁵	Malawi	Case-control	February 2004-September 2005	351 cases	1729 controls	PTB	Rural setting, high HIV prevalence (26.2%), singleton pregnancies.	No description on HIV disease stage. HIV-diagnoses made after delivery, hence no antenatal ART.	Risk factor analysis, regression analysis	Late ultrasound	Average
Europe											
Bucceri et al 1997 ⁴⁶	Italy	Prospective cohort	1985-1993	151	164	PTB, LBW	Urban setting. Intravenous drug users. All women delivered in hospital.	93% of women were asymptomatic (CDC stage A) and 5% had a CD4 < 200 cells/μl. ART not yet demonstrated to be effective in pregnancy.	Regression analysis	Neonatal assessment (not specified), LNMP and late ultrasound	Average
Johnstone et al 1996 ⁴⁷	United Kingdom	Retrospective cohort	1983-1992	82	302	PTB	Intravenous drug users or sexual partners of intravenous drug user. Singleton pregnancies.	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	Matching, regression analysis	Late ultrasound and LNMP	Poor
The Americas and Caribbean											
Alger et al 1993 ⁴⁸	USA	Prospective cohort	July 1987-July 1991	101	97	LBW	Low SES, inner city. Current or former intravenous drug users or sexual partners of intravenous drug users.	One woman with an AIDS defining opportunistic infection and 15.8% of women had a CD4 count < 200 cells/μl. ART not yet demonstrated to be effective in pregnancy.	Risk factor analysis	Unspecified	Average

Ellis et al 2002 ⁴⁹	USA	Retrospective cohort	January 1988- December 1995	563	2252	PTB, LBW, SGA	Low SES, inner city. Referral centre for high-risk obstetric patients. All women delivered in hospital.	No description on HIV disease stage. ART not yet recommended in pregnancy in national guideline.	Regression analysis	Unspecified	Poor
Halsey et al 1990 ⁵⁰	Haiti	Prospective cohort	August 1986- August 1988	199	1994	PTB, LBW	Low SES, with no history of intravenous drug use or cocaine. Sample was representative of the community.	All women were asymptomatic. ART not yet demonstrated to be effective in pregnancy.	None	Neonatal assessment (Dubowitz)	Average
Markson et al 1996 ⁵¹	USA	Retrospective cohort	1989-1990	772	2377	PTB, LBW, Term-LBW	Urban setting, singleton pregnancy. Data drawn from New York city Medicaid claims database	No description on HIV disease stage. ART not yet demonstrated to be effective in pregnancy.	Matching, risk factor analysis, regression analysis	LNMP	Poor
Maynard et al 1990 ⁵²	USA	Retrospective cohort	March 1985- February 1988	17	41	PTB, LBW, VLBW	Intravenous drug users. All women delivered in hospital.	82.4% of women were asymptomatic and 17.6% were symptomatic. ART not yet demonstrated to be effective in pregnancy.	None	Unspecified	Average
Selwyn et al 1989 ⁵³	USA	Prospective cohort	June 1985-1988	39	58	Term-LBW, MC	Inner city intravenous drug users. All women delivered in hospital.	54% of women were asymptomatic (CDC II), 42% had persistent generalised lymphadenopathy (CDC III), 4% had advanced disease (CDC IV C.2) and none of the women met the criteria for AIDS. ART not yet demonstrated to be effective in pregnancy.	None	Unspecified	Poor
Asia											

Kumar et al 1995 ⁵⁴	India	Prospective cohort	January 1992- January 1993	150	152	PTB, LBW, SGA	Low SES, no illicit drug use, referral hospital. All women delivered in hospital.	53% of women were asymptomatic (CDC I/II), 38% were symptomatic (CDC III) and 9% met the criteria for AIDS (CDC IV). ART not yet demonstrated to be effective in pregnancy.	Matching, risk factor analysis	Neonatal assessment (Dubowitz)	Average
Mitgitti et al 2008 ⁵⁵	Thailand	Retrospective cohort	January 1997- December 2002	266	5872	PTB, LBW	Singleton pregnancies. All women delivered in hospital.	No description on HIV disease stage or why ART not provided.	Risk factor analysis, regression	Unspecified	Poor

Figure

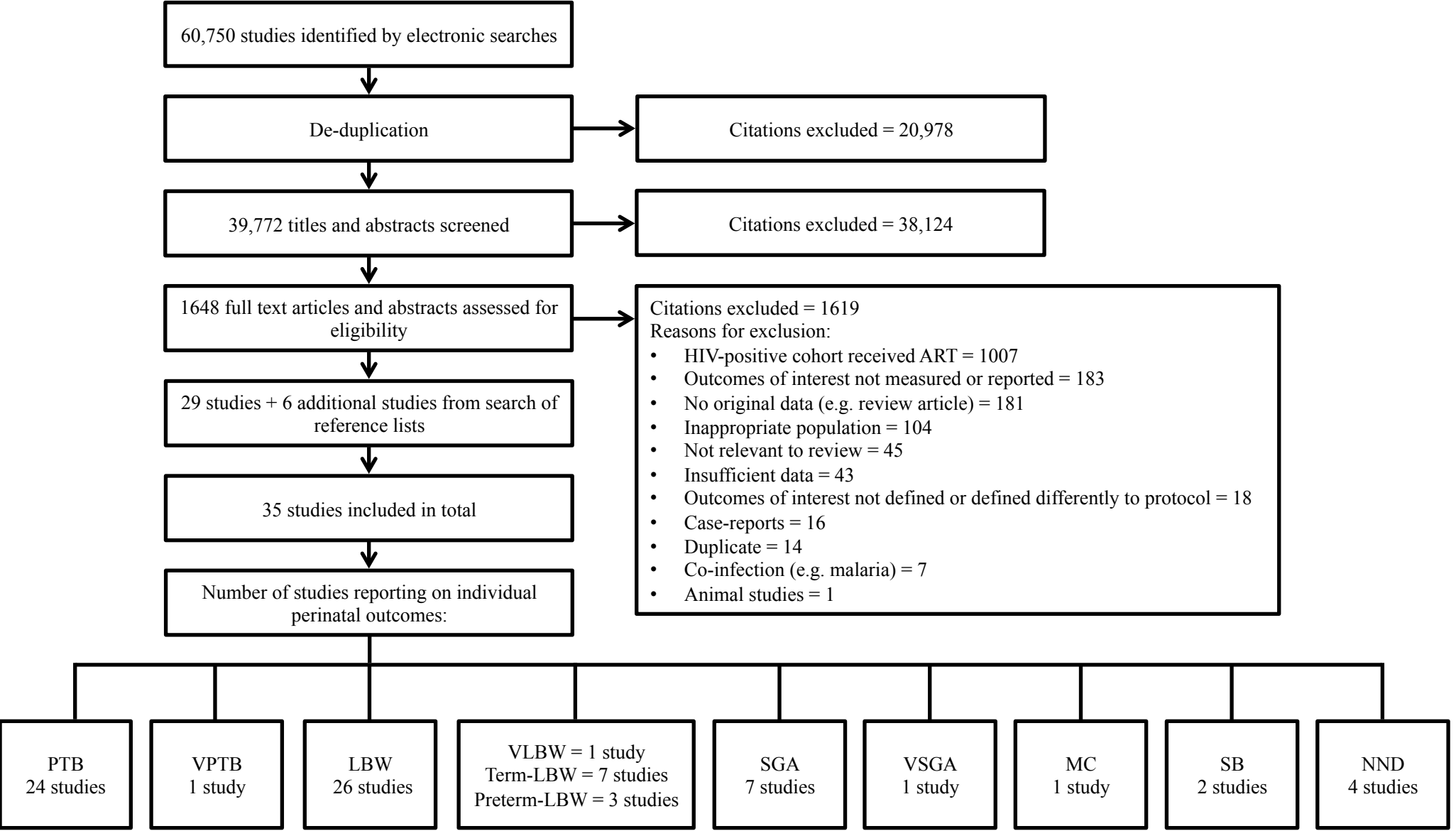


Figure 1. Schematic representation of study selection process.

Perinatal outcome	Cohort design	RR (95% CI)	Studies (n)	HIV-positive participants (%)	Total participants (n)
PTB	Prospective	1.50 (1.24, 1.82)	14	4632 (39)	11870
	Retrospective	1.82 (1.41, 2.34)	8	2533 (13)	19894
VPTB	Prospective	0.99 (0.60, 1.65)	1	1189 (50)	2368
LBW	Prospective	1.62 (1.41, 1.86)	16	4963 (37)	13382
	Retrospective	1.93 (1.48, 2.52)	9	3921 (17)	22828
VLBW	Retrospective	4.82 (0.47, 49.72)	1	17 (29)	58
Term-LBW	Prospective	1.30 (0.98, 1.72)	5	1326 (45)	2978
	Retrospective	2.62 (1.15, 5.93)	2	1235 (30)	4060
Preterm-LBW	Prospective	1.18 (0.91, 1.54)	2	468 (54)	860
	Retrospective	3.25 (2.12, 4.99)	1	663 (50)	1339
SGA	Prospective	1.31 (1.14, 1.51)	4	2024 (40)	5086
	Retrospective	2.08 (1.26, 3.46)	3	752 (8)	9229
VSGA	Prospective	1.28 (0.95, 1.71)	1	1189 (50)	2368
MC	Prospective	1.40 (0.37, 5.36)	1	52 (42)	125
SB	Prospective	1.67 (1.05, 2.66)	2	583 (50)	1168
NND	Prospective	1.68 (0.45, 6.29)	3	1043 (47)	2231
	Retrospective	2.00 (0.61, 6.54)	1	218 (50)	436

NOTE: Weights are from random effects analysis

Figure 2. Perinatal outcomes associated with ART-naïve maternal HIV infection, by study design.

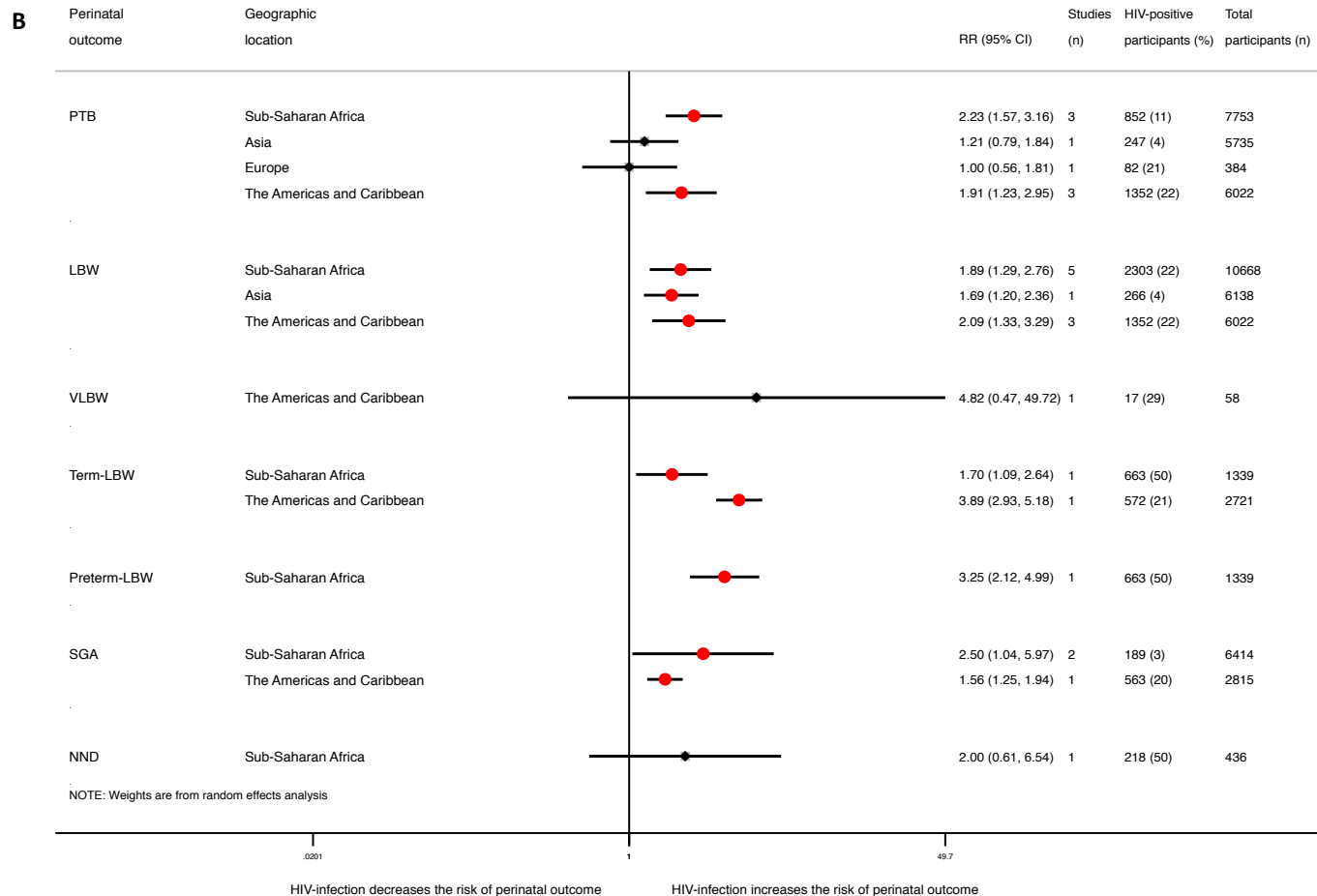
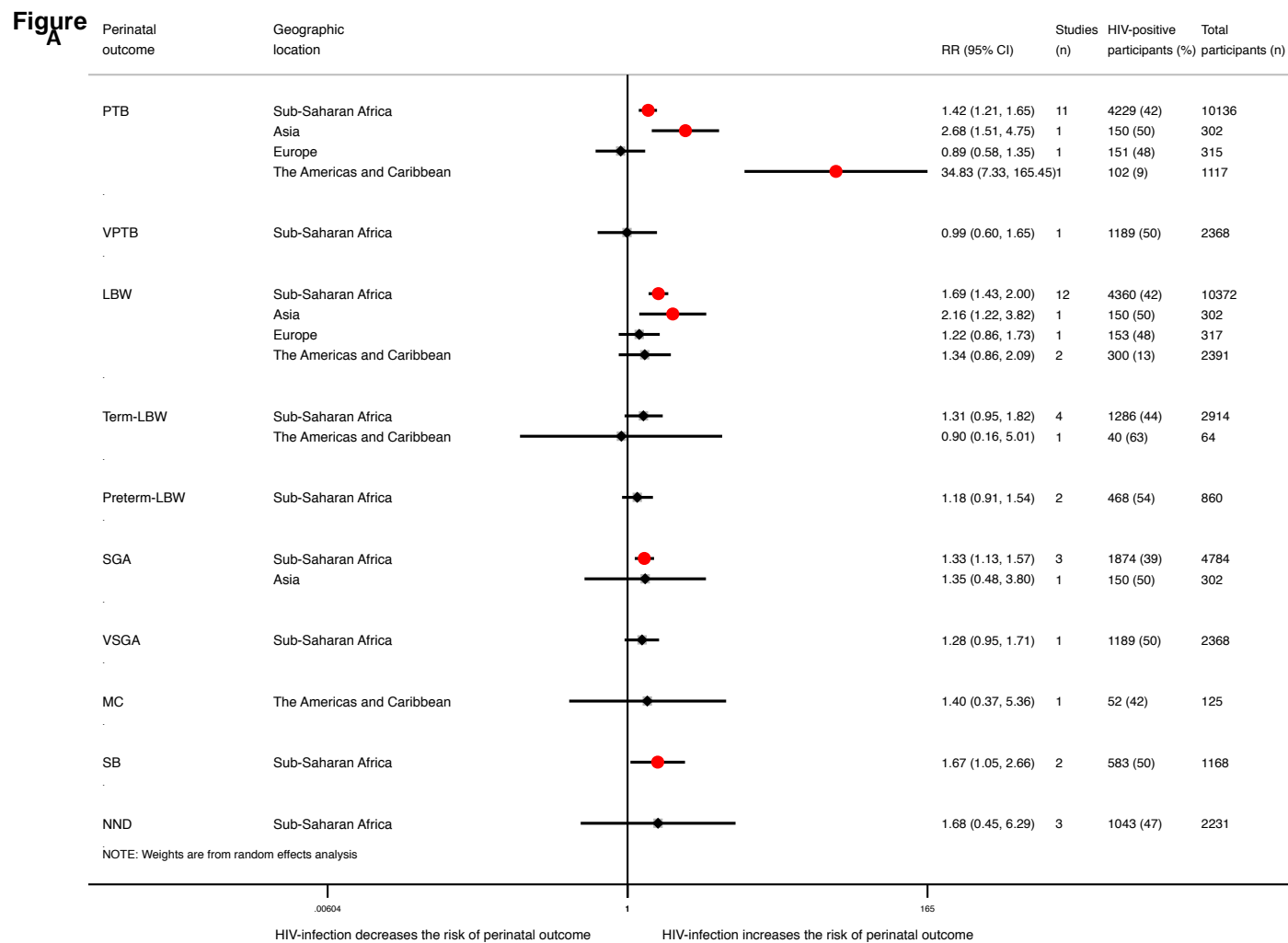
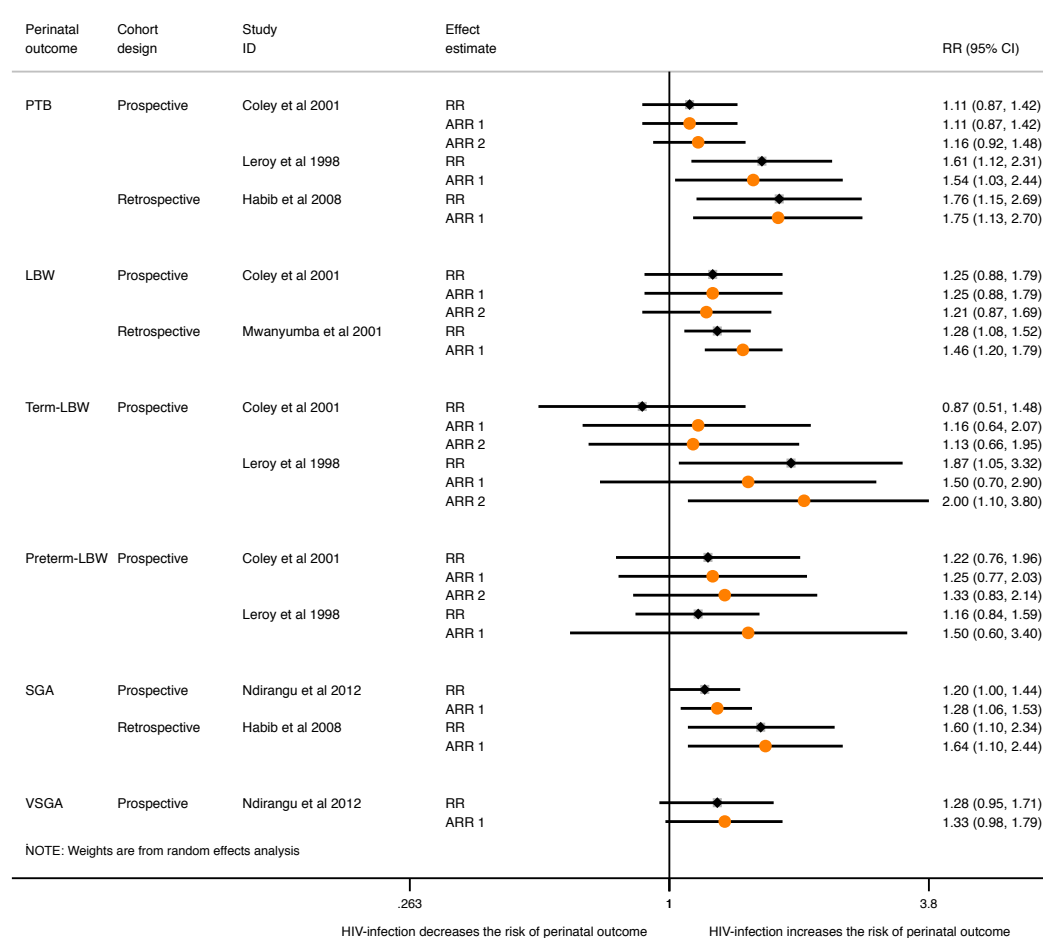


Figure 3. Perinatal outcomes associated with ART-naïve maternal HIV infection, by geographic region. A: Prospective cohort studies, B: Retrospective cohort studies.

Figure



B

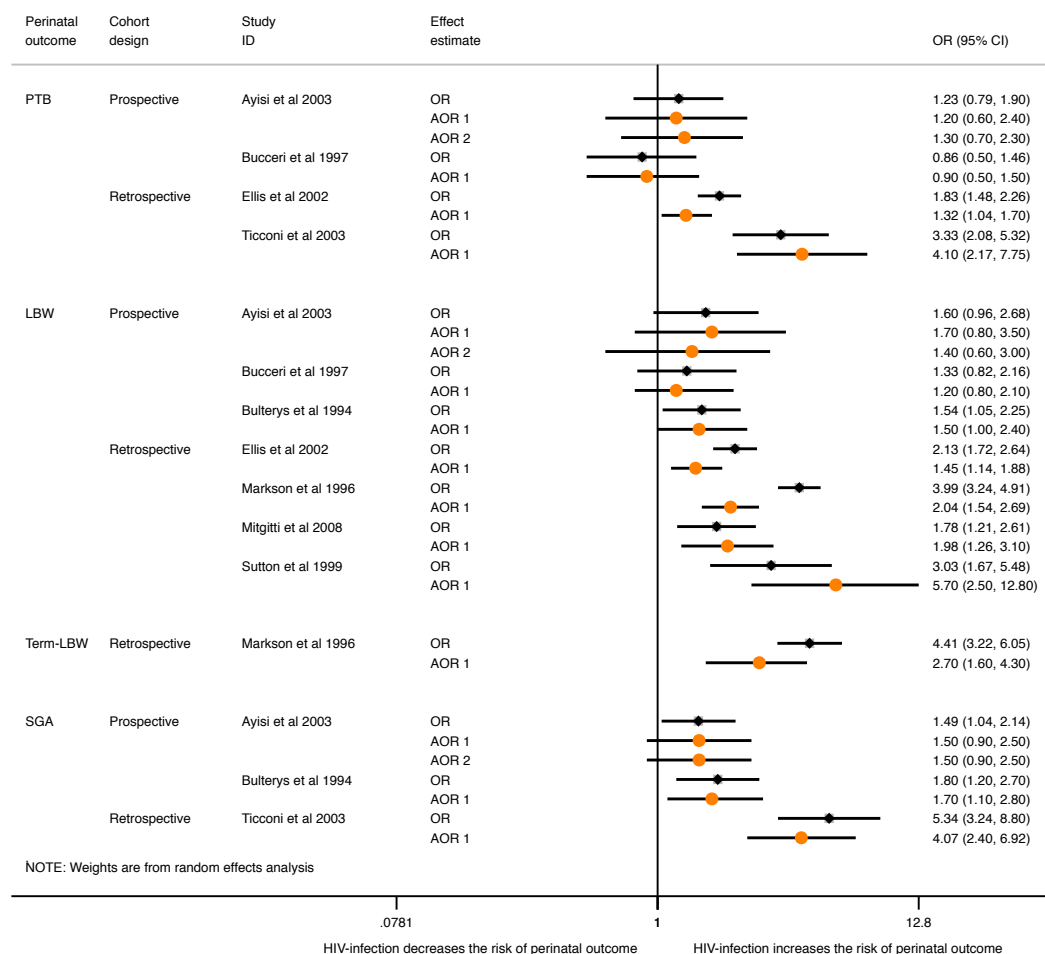


Figure 4. Sensitivity analysis of the adjustment for confounding factors in studies that assessed the association between ART-naïve maternal HIV-infection and perinatal outcomes. A: relative risk (RR) estimates, B: odds ratio (OR) estimates.

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Systematic review and meta-analysis of perinatal outcomes associated with maternal HIV-infection.

Appendices

Appendix 1.

Literature search strategy for specific perinatal outcomes.

Embase search strategy for “preterm birth or low birth weight or intrauterine growth restriction or stillbirth” and “HIV or ART”. Search carried out on 20 February 2013 and rerun on 12 December 2014 (limited to the years 2013 or 2014 only) to include studies published between 1 January 1980 and 7 December 2014. Embase (OVID 1974 to 2013 Week 07):

1. Prematurity/
2. Premature labor/
3. Premature fetus membrane rupture/
4. Immature and premature labor/
5. 'premature birth'.ti,ab.
6. 'prematurity'.ti,ab.
7. 'gestational age at birth'.ti,ab.
8. 'gestational age at delivery'.ti,ab.
9. (PTB or PTBS).ti,ab.
10. (VPTB or VPTBs).ti,ab.
11. (pre-terms or preterms).ti,ab.
12. (pre-term adj (birth or births)).ti,ab.
13. (preterm adj (birth or births)).ti,ab.
14. (premature adj (birth or births)).ti,ab.
15. (PTL or PTLs).ti,ab.
16. (VPTL or VPTLs).ti,ab.
17. ((pre-term or preterm) adj (labor* or labour*)).ti,ab.
18. (pre-term adj obstetric adj labor*).ti,ab.
19. (pre-term adj obstetric adj labour*).ti,ab.
20. (preterm adj obstetric adj labor*).ti,ab.
21. (preterm adj obstetric adj labour*).ti,ab.
22. (premature adj (labor* or labour*)).ti,ab.
23. (premature adj obstetric adj labor*).ti,ab.
24. (premature adj obstetric adj labour*).ti,ab.
25. (PTD or PTDs).ti,ab.
26. (VPTD or VPTDs).ti,ab.
27. ((pre-term or preterm) adj deliver*).ti,ab.
28. ((pre-term or preterm) adj infant*).ti,ab.
29. (premature adj (deliver* or infant*)).ti,ab.
30. (PROM or PPROM).ti,ab.
31. 'preterm rupture of membranes'.ti,ab.
32. 'preterm rupture of fetal membranes'.ti,ab.
33. 'preterm rupture of foetal membranes'.ti,ab.
34. 'pre-term rupture of membranes'.ti,ab.
35. 'pre-term rupture of fetal membranes'.ti,ab.
36. 'pre-term rupture of foetal membranes'.ti,ab.
37. 'premature rupture of membranes'.ti,ab.
38. 'premature rupture of fetal membranes'.ti,ab.
39. 'premature rupture of foetal membranes'.ti,ab.
40. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. Intrauterine growth retardation/
42. Small for date infant/
43. Low birth weight/
44. Very low birthweight/
45. Extremely low birth weight/
46. (IUGR or FGR).ti,ab.
47. ((intrauterine or intra-uterine) adj growth adj restriction).ti,ab.
48. ((intrauterine or intra-uterine) adj growth adj restricted).ti,ab.

49. ((intrauterine or intra-uterine) adj growth adj retardation).ti,ab.
50. 'fetal growth restriction'.ti,ab.
51. 'fetal growth restricted'.ti,ab.
52. 'fetal growth retardation'.ti,ab.
53. (SGA or SFGA).ti,ab.
54. 'small for gestational age'.ti,ab.
55. 'small-for-gestational-age'.ti,ab.
56. 'small-for-gestational age'.ti,ab.
57. 'small for gestation'.ti,ab.
58. 'small-for-gestation'.ti,ab.
59. (VSGA or SFD).ti,ab.
60. 'very-small-for-gestational-age'.ti,ab.
61. 'very-small-for-gestational age'.ti,ab.
62. 'small for dates'.ti,ab.
63. 'small-for-dates'.ti,ab.
64. 'weight for dates'.ti,ab.
65. 'weight for gestational age'.ti,ab.
66. 'weight for age at delivery'.ti,ab.
67. 'weight at delivery'.ti,ab.
68. 'birthweight for dates'.ti,ab.
69. 'birthweight for gestational age'.ti,ab.
70. 'birthweight for age at delivery'.ti,ab.
71. 'birth weight for dates'.ti,ab.
72. 'birth weight for gestational age'.ti,ab.
73. 'birth weight for age at delivery'.ti,ab.
74. 'birth-weight for dates'.ti,ab.
75. 'birth-weight for gestational age'.ti,ab.
76. 'birth-weight for age at delivery'.ti,ab.
77. LBW.ti,ab.
78. 'low BW'.ti,ab.
79. 'low birth weight'.ti,ab.
80. 'low birth-weight'.ti,ab.
81. 'low-birth weight'.ti,ab.
82. 'low-birth-weight'.ti,ab.
83. 'low birthweight'.ti,ab.
84. 'low-birthweight'.ti,ab.
85. 'lower BW'.ti,ab.
86. 'lower birth weight'.ti,ab.
87. 'lower birth-weight'.ti,ab.
88. 'lower-birth weight'.ti,ab.
89. 'lower-birth-weight'.ti,ab.
90. 'lower birthweight'.ti,ab.
91. 'lower-birthweight'.ti,ab.
92. 'reduced birth weight'.ti,ab.
93. 'reduced birthweight'.ti,ab.
94. 'reduced birth-weight'.ti,ab.
95. (VLBW or ELBW).ti,ab.
96. 'very-low birthweight'.ti,ab.
97. 'very-low birth weight'.ti,ab.
98. 'very-low birth-weight'.ti,ab.
99. 'very-low-birthweight'.ti,ab.
100. 'very-low-birth-weight'.ti,ab.
101. 'extremely-low birthweight'.ti,ab.
102. 'extremely-low birth weight'.ti,ab.
103. 'extremely-low birth-weight'.ti,ab.
104. 'extremely-low-birthweight'.ti,ab.
105. 'extremely-low-birth-weight'.ti,ab.
106. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105
107. Stillbirth/
108. Fetus death/
109. (stillbirth* or stillborn*).ti,ab.
110. (still adj (born* or birth*)).ti,ab.
111. (abortion* or miscarriage*).ti,ab.

112. (pregnancy adj (death* or loss* or demise* or mortalit*)).ti,ab.
 113. (gestational adj (death* or loss* or demise* or mortalit*)).ti,ab.
 114. (fetal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 115. (foetal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 116. (obstetric* adj (death* or loss* or demise* or mortalit*)).ti,ab.
 117. (labor adj (death* or loss* or demise* or mortalit*)).ti,ab.
 118. (birth adj (death* or loss* or demise* or mortalit*)).ti,ab.
 119. (delivery adj (death* or loss* or demise* or mortalit*)).ti,ab.
 120. (neonat* adj (death* or loss* or demise* or mortalit*)).ti,ab.
 121. (newborn adj (death* or loss* or demise* or mortalit*)).ti,ab.
 122. (new-born adj (death* or loss* or demise* or mortalit*)).ti,ab.
 123. (new adj born adj death*).ti,ab.
 124. (new adj born adj loss*).ti,ab.
 125. (new adj born adj demise*).ti,ab.
 126. (new adj born adj mortalit*).ti,ab.
 127. (infant adj (death* or loss* or demise* or mortalit*)).ti,ab.
 128. (reproductive adj (death* or loss* or demise* or mortalit*)).ti,ab.
 129. (prelabor adj (death* or loss* or demise* or mortalit*)).ti,ab.
 130. (pre-labor adj (death* or loss* or demise* or mortalit*)).ti,ab.
 131. (intrauterine adj (death* or loss* or demise* or mortalit*)).ti,ab.
 132. (intra-uterine adj (death* or loss* or demise* or mortalit*)).ti,ab.
 133. (antenatal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 134. (ante-natal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 135. (prenatal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 136. (pre-natal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 137. (perinatal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 138. (peri-natal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 139. (neo-natal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 140. (postnatal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 141. (post-natal adj (death* or loss* or demise* or mortalit*)).ti,ab.
 142. (antepartum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 143. (ante-partum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 144. (intrapartum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 145. (intra-partum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 146. (peripartum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 147. (peri-partum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 148. (postpartum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 149. (post-partum adj (death* or loss* or demise* or mortalit*)).ti,ab.
 150. 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149
 151. Human immunodeficiency virus/
 152. Human immunodeficiency virus 1/
 153. Human immunodeficiency virus 1 infection/
 154. Human immunodeficiency virus 2/
 155. Human immunodeficiency virus 2 infection/
 156. Human immunodeficiency virus infection/
 157. Human immunodeficiency virus infected patient/
 158. Acquired immune deficiency syndrome/
 159. Serodiagnosis/
 160. HIV associated dementia/
 161. HIV associated lipodystrophy/
 162. HIV associated nephropathy/
 163. AIDS related complex/
 164. 'HIV seropositivity'.ti,ab.
 165. 'HIV infection*'.ti,ab.
 166. 'AIDS serodiagnosis'.ti,ab.
 167. 'AIDS arteritis'.ti,ab.
 168. 'AIDS-associated nephropathy'.ti,ab.
 169. 'AIDS dementia complex'.ti,ab.
 170. 'AIDS-related opportunistic infection*'.ti,ab.
 171. 'AIDS-related lymphoma'.ti,ab.
 172. (HIV or HIV-1 or HIV-type-1).ti,ab.
 173. 'HTLV III'.ti,ab.
 174. 'HTLV type III'.ti,ab.

175. (HTLV-III or HTLV-type-III or LAV or HTLV-III-LAV or LAV-HTLV-III).ti,ab.
176. (HIV-2 or HIV-type-2 or HIV-II or HTLV-IV or LAV-2).ti,ab.
177. (HIV-positive or HIV-1-positive or HIV-2-positive or HIV-infected).ti,ab.
178. (HIV-1-infected or HIV-type-1-infected or HTLV-III-infected or HTLV-type-III-infected or LAV-infected).ti,ab.
179. 'HTLV III-infected'.ti,ab.
180. 'HTLV type III-infected'.ti,ab.
181. (HTLV-III-LAV-infected or LAV-HTLV-III-infected or HIV-2-infected or HIV-type-2-infected or HIV-II-infected).ti,ab.
182. (HTLV-IV-infected or LAV-2-infected or HIV-infection* or HIV-1-infection* or HIV-type-1-infection* or HTLV-III-infection* or HTLV-type-III-infection*).ti,ab.
183. 'HTLV III-infection*.ti,ab.
184. 'HTLV type III-infection*.ti,ab.
185. (LAV-infection* or HTLV-III-LAV-infection* or LAV-HTLV-III-infection* or HIV-2-infection* or HIV-type-2-infection* or HIV-II-infection* or HTLV-IV-infection* or LAV-2-infection*).ti,ab.
186. 'Human Immunodeficiency Virus*.ti,ab.
187. 'Human Immune Deficiency Virus*.ti,ab.
188. 'Human T Cell Lymphotropic Virus Type III'.ti,ab.
189. 'Human T-Cell Lymphotropic Virus Type III'.ti,ab.
190. 'Human T Lymphotropic Virus Type III'.ti,ab.
191. 'Human T-Lymphotropic Virus Type III'.ti,ab.
192. 'Human T Lymphotropic Virus Type IV'.ti,ab.
193. 'Human T-Lymphotropic Virus Type IV'.ti,ab.
194. 'Human T Cell Leukemia Virus Type III'.ti,ab.
195. 'Human T-Cell Leukemia Virus Type III'.ti,ab.
196. 'Lymphadenopathy-Associated Virus*.ti,ab.
197. 'Lymphadenopathy Associated Virus*.ti,ab.
198. 'Acquired Immune Deficiency Syndrome'.ti,ab.
199. 'Acquired Immunodeficiency Syndrome'.ti,ab.
200. AIDS.ti,ab.
201. 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200
202. Human immunodeficiency virus antibody/
203. Human immunodeficiency virus antigen/
204. exp Human immunodeficiency virus fusion inhibitor/
205. exp Human immunodeficiency virus proteinase inhibitor/
206. exp Anti human immunodeficiency virus agent/
207. exp Integrase inhibitor/
208. exp RNA directed DNA polymerase inhibitor/
209. Antiretrovirus agent/
210. Proteinase inhibitor/
211. (antiretroviral* or anti-retroviral*).ti,ab.
212. (antiretroviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
213. (anti-retroviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
214. (antiviral* or anti-viral*).ti,ab.
215. (antiviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
216. (anti-viral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
217. (anti-HIV adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
218. (HIV adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
219. (anti-HIV-1 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
220. (HIV-1 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
221. (anti-HIV-2 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
222. (HIV-2 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
223. (anti-AIDS adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
224. (AIDS adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
225. (HAART or ARV or ARVs or cARV or cARVs).ti,ab.
226. (HAART-exposed or HAART-treated or Mega-HAART).ti,ab.
227. (ARV-exposed or ARV-treated or combination-ARV or combination-ARVs or combined-ARV or combined-ARVs).ti,ab.
228. (ART or Multi-ART or Triple-ART or cART or ART-exposed or ART-treated or combination-ART or combined-ART or sc-ART).ti,ab.
229. 'short-course-antiretroviral therap*.ti,ab.
230. 'short-course-anti-retroviral therap*.ti,ab.
231. (combination adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
232. (combined adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
233. (monotherapy* or mono-therap*).ti,ab.
234. 'dual therap*.ti,ab.

235. 'dual drug therap*'.ti,ab.
 236. bitherap*.ti,ab.
 237. (PI or PIs or PI-based or PI-boosted or PI-containing or PI-therap* or PI-treatment* or PI-regimen*).ti,ab.
 238. (Ritonavir-boosted or NRTI or NRTIs or NRTI-based).ti,ab.
 239. 'protease inhibitor*'.ti,ab.
 240. (NRTI-containing or NRTI-therap* or NRTI-treatment* or NRTI-regimen*).ti,ab.
 241. 'nucleoside reverse transcriptase inhibitor*'.ti,ab.
 242. 'nucleoside analog reverse transcriptase inhibitor*'.ti,ab.
 243. (NNRTI or NNRTIs or NNRTI-based or NNRTI-containing or NNRTI-therap* or NNRTI-treatment* or NNRTI-regimen*).ti,ab.
 244. 'non nucleoside reverse transcriptase inhibitor*'.ti,ab.
 245. 'non-nucleoside reverse transcriptase inhibitor*'.ti,ab.
 246. 'nonnucleoside reverse transcriptase inhibitor*'.ti,ab.
 247. 'non nucleoside analog reverse transcriptase inhibitor*'.ti,ab.
 248. 'non-nucleoside analog reverse transcriptase inhibitor*'.ti,ab.
 249. 'nonnucleoside analog reverse transcriptase inhibitor*'.ti,ab.
 250. (NtRTI or NtRTIs or NtRTI-based or NtRTI-containing or NtRTI-therap* or NtRTI-treatment* or NtRTI-regimen*).ti,ab.
 251. 'nucleotide reverse transcriptase inhibitor*'.ti,ab.
 252. 'nucleotide analog reverse transcriptase inhibitor*'.ti,ab.
 253. 'fusion inhibitor*'.ti,ab.
 254. 'CCR5 receptor antagonist*'.ti,ab.
 255. 'integrase inhibitor*'.ti,ab.
 256. 'maturation inhibitor*'.ti,ab.
 257. 'entry inhibitor*'.ti,ab.
 258. (Abacavir or ABC).tw.
 259. Abacavir/
 260. Abacavir plus lamivudine/
 261. Abacavir plus lamivudine plus zidovudine/
 262. (Didanosine or ddI).tw.
 263. Didanosine/
 264. (Emtricitabine or FTC).tw.
 265. Emtricitabine/
 266. Efavirenz plus emtricitabine plus tenofovir disoproxil/
 267. Emtricitabine plus rilpivirine plus tenofovir disoproxil/
 268. Emtricitabine plus tenofovir disoproxil/
 269. (Lamivudine or 3TC).tw.
 270. Lamivudine/
 271. Efavirenz plus lamivudine plus zidovudine/
 272. Lamivudine plus nevirapine plus stavudine/
 273. Lamivudine plus nevirapine plus tenofovir disoproxil/
 274. Lamivudine plus nevirapine plus zidovudine/
 275. Lamivudine plus stavudine/
 276. Lamivudine plus tenofovir disoproxil/
 277. Lamivudine plus zidovudine/
 278. (Stavudine or d4T).tw.
 279. Stavudine/
 280. (Tenofovir or TFV or TDF).tw.
 281. Tenofovir/
 282. Cobicistat plus elvitegravir plus emtricitabine plus tenofovir disoproxil/
 283. Tenofovir disoproxil/
 284. Tenofovir 3 hexadecyloxypropyl ester/
 285. Tenofovir alafenamide/
 286. (Zidovudine or AZT or ZDV).tw.
 287. Zidovudine/
 288. Zidovudine 5' phosphate/
 289. Zidovudine 5' triphosphate/
 290. Zidovudine derivative/
 291. Zidovudine glucuronide/
 292. (Delavirdine or DLV).tw.
 293. Delavirdine/
 294. (Efavirenz or EFV).tw.
 295. Efavirenz/
 296. (Etravirine or ETR).tw.
 297. Etravirine/
 298. (Nevirapine or NVP).tw.

299. Nevirapine/
 300. (Rilpivirine or RPV).tw.
 301. Rilpivirine/
 302. (Atazanavir or ATV).tw.
 303. (Atazanavir/Ritonavir).tw.
 304. (ATV/r).tw.
 305. Atazanavir/
 306. Atazanavir plus ritonavir/
 307. (Darunavir or DRV).tw.
 308. (Darunavir adj Ritonavir).tw.
 309. (DRV adj r).tw.
 310. Darunavir/
 311. Darunavir plus ritonavir/
 312. (Fosamprenavir or FPV).tw.
 313. (Fosamprenavir adj Ritonavir).tw.
 314. (FPV adj r).tw.
 315. Fosamprenavir/
 316. Fosamprenavir plus ritonavir/
 317. (Indinavir or IDV).tw.
 318. (Indinavir adj Ritonavir).tw.
 319. (IDV adj r).tw.
 320. Indinavir/
 321. Indinavir plus ritonavir/
 322. (Lopinavir or LPV).tw.
 323. (Lopinavir adj Ritonavir).tw.
 324. (LPV adj r).tw.
 325. Lopinavir/
 326. Lopinavir plus ritonavir/
 327. (Nelfinavir or NFV).tw.
 328. (Nelfinavir adj Ritonavir).tw.
 329. (NFV adj r).tw.
 330. Nelfinavir/
 331. (Ritonavir or RTV).tw.
 332. Ritonavir/
 333. (Saquinavir or SQV).tw.
 334. (Saquinavir adj Ritonavir).tw.
 335. (SQV adj r).tw.
 336. Saquinavir/
 337. Ritonavir plus saquinavir/
 338. (Tipranavir or TPV).tw.
 339. (Tipranavir adj Ritonavir).tw.
 340. (TPV adj r).tw.
 341. Tipranavir/
 342. Ritonavir plus tipranavir/
 343. (Enfuvirtide or T-20).tw.
 344. Enfuvirtide/
 345. (Maraviroc or MVC).tw.
 346. Maraviroc/
 347. (Raltegravir or RAL).tw.
 348. Raltegravir/
 349. (Elvitegravir or EVG).tw.
 350. Elvitegravir/
 351. (Zalcitabine or ddC).tw.
 352. Zalcitabine/
 353. (Combivir or Trizivir or Kaletra or Epzicom or Kivexa or Truvada or Atripla).tw.
 354. 202 or 203 or 204 or 305 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257 or 258 or 259 or 260 or 261 or 262 or 263 or 264 or 265 or 266 or 267 or 268 or 269 or 270 or 271 or 272 or 273 or 274 or 275 or 276 or 277 or 278 or 279 or 280 or 281 or 282 or 283 or 284 or 285 or 286 or 287 or 288 or 289 or 290 or 291 or 292 or 293 or 294 or 295 or 296 or 297 or 298 or 299 or 300 or 301 or 302 or 303 or 304 or 305 or 306 or 307 or 308 or 309 or 310 or 311 or 312 or 313 or 314 or 315 or 316 or 317 or 318 or 319 or 320 or 321 or 322 or 323 or 324 or 325 or 326 or 327 or 328 or 329 or 330 or 331 or 332 or 333 or 334 or 335 or 336 or 337 or 338 or 339 or 340 or 341 or 342 or 343 or 344 or 345 or 346 or 347 or 348 or 349 or 350 or 351 or 352 or 353
 355. 40 OR 106 OR 150

356. 201 OR 354
357. 355 AND 356
358. limit 357 to yr=1980-2013

Appendix 2.

Literature search strategy for general perinatal outcomes.

Embase search strategy for “pregnancy outcome” and “HIV or ART”. Search carried out on 20 February 2013 and rerun on 12 December 2014 (limited to the years 2013 or 2014 only) to include studies published between 1 January 1980 and 7 December 2014. Embase (OVID 1974 to 2013 Week 11).

1. Pregnancy outcome/
2. Pregnancy complication/
3. (pregnancy adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
4. (gestational adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
5. Fetus outcome/
6. (fetal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
7. (foetal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
8. (obstetric adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
9. (obstetrical adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
10. Labor complication/
11. (labor adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
12. (labour adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
13. (birth adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
14. (delivery adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
15. (neonate adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
16. (newborn adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
17. (new-born adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
18. "new born outcome*".ti,ab.
19. "new born complication*".ti,ab.
20. "new born consequence*".ti,ab.
21. "new born characteristic*".ti,ab.
22. "new born event*".ti,ab.
23. "new born result*".ti,ab.
24. "new born problem*".ti,ab.
25. "new born morbidit*".ti,ab.
26. "new born sequelae*".ti,ab.
27. (infant adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
28. (reproductive adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
29. (prelabour adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
30. (prelabor adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
31. (pre-labour adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
32. (pre-labor adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
33. (intrauterine adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
34. (intra-uterine adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
35. (antenatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.

36. (ante-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
37. (prenatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
38. (pre-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
39. Perinatal morbidity/
40. (perinatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
41. (peri-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
42. (neonatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
43. (neo-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
44. (postnatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
45. (post-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
46. (antepartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
47. (ante-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
48. (intrapartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
49. (intra-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
50. (peripartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
51. (peri-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
52. (postpartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
53. (post-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidity* or sequelae)).ti,ab.
54. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. Human immunodeficiency virus/
56. Human immunodeficiency virus 1/
57. Human immunodeficiency virus 1 infection/
58. Human immunodeficiency virus 2/
59. Human immunodeficiency virus 2 infection/
60. Human immunodeficiency virus infection/
61. Human immunodeficiency virus infected patient/
62. Acquired immune deficiency syndrome/
63. Serodiagnosis/
64. HIV associated dementia/
65. HIV associated lipodystrophy/
66. HIV associated nephropathy/
67. AIDS related complex/
68. 'HIV seropositivity'.ti,ab.
69. 'HIV infection*.ti,ab.
70. 'AIDS serodiagnosis'.ti,ab.
71. 'AIDS arteritis'.ti,ab.
72. 'AIDS-associated nephropathy'.ti,ab.
73. 'AIDS dementia complex'.ti,ab.
74. 'AIDS-related opportunistic infection*.ti,ab.
75. 'AIDS-related lymphoma'.ti,ab.
76. (HIV or HIV-1 or HIV-type-1).ti,ab.
77. 'HTLV III'.ti,ab.
78. 'HTLV type III'.ti,ab.
79. (HTLV-III or HTLV-type-III or LAV or HTLV-III-LAV or LAV-HTLV-III).ti,ab.
80. (HIV-2 or HIV-type-2 or HIV-II or HTLV-IV or LAV-20).ti,ab.
81. (HIV-positive or HIV-1-positive or HIV-2-positive or HIV-infected).ti,ab.

82. (HIV-1-infected or HIV-type-1-infected or HTLV-III-infected or HTLV-type-III-infected or LAV-infected).ti,ab.
83. 'HTLV III-infected'.ti,ab.
84. 'HTLV type III-infected'.ti,ab.
85. (HTLV-III-LAV-infected or LAV-HTLV-III-infected or HIV-2-infected or HIV-type-2-infected or HIV-II-infected).ti,ab.
86. (HTLV-IV-infected or LAV-2-infected or HIV-infection* or HIV-1-infection* or HIV-type-1-infection* or HTLV-III-infection* or HTLV-type-III-infection*).ti,ab.
87. 'HTLV III-infection*.ti,ab.
88. 'HTLV type III-infection*.ti,ab.
89. (LAV-infection* or HTLV-III-LAV-infection* or LAV-HTLV-III-infection* or HIV-2-infection* or HIV-type-2-infection* or HIV-II-infection* or HTLV-IV-infection* or LAV-2-infection*).ti,ab.
90. 'Human Immunodeficiency Virus*.ti,ab.
91. 'Human Immune Deficiency Virus*.ti,ab.
92. 'Human T Cell Lymphotropic Virus Type III'.ti,ab.
93. 'Human T-Cell Lymphotropic Virus Type III'.ti,ab.
94. 'Human T Lymphotropic Virus Type III'.ti,ab.
95. 'Human T-Lymphotropic Virus Type III'.ti,ab.
96. 'Human T Lymphotropic Virus Type IV'.ti,ab.
97. 'Human T-Lymphotropic Virus Type IV'.ti,ab.
98. 'Human T Cell Leukemia Virus Type III'.ti,ab.
99. 'Human T-Cell Leukemia Virus Type III'.ti,ab.
100. 'Lymphadenopathy-Associated Virus*.ti,ab.
101. 'Lymphadenopathy Associated Virus*.ti,ab.
102. 'Acquired Immune Deficiency Syndrome'.ti,ab.
103. 'Acquired Immunodeficiency Syndrome'.ti,ab.
104. AIDS.ti,ab.
105. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104
106. Human immunodeficiency virus antibody/
107. Human immunodeficiency virus antigen/
108. exp Human immunodeficiency virus fusion inhibitor/
109. exp Human immunodeficiency virus proteinase inhibitor/
110. exp Anti human immunodeficiency virus agent/
111. exp Integrase inhibitor/
112. exp RNA directed DNA polymerase inhibitor/
113. Antiretrovirus agent/
114. Proteinase inhibitor/
115. (antiretroviral* or anti-retroviral*).ti,ab.
116. (antiretroviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
117. (anti-retroviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
118. (antiviral* or anti-viral*).ti,ab.
119. (antiviral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
120. (anti-viral adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
121. (anti-HIV adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
122. (HIV adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
123. (anti-HIV-1 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
124. (HIV-1 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
125. (anti-HIV-2 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
126. (HIV-2 adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
127. (anti-AIDS adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
128. (AIDS adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
129. (HAART or ARV or ARVs or cARV or cARVs).ti,ab.
130. (HAART-exposed or HAART-treated or Mega-HAART).ti,ab.
131. (ARV-exposed or ARV-treated or combination-ARV or combination-ARVs or combined-ARV or combined-ARVs).ti,ab.
132. (ART or Multi-ART or Triple-ART or cART or ART-exposed or ART-treated or combination-ART or combined-ART or sc-ART).ti,ab.
133. 'short-course-antiretroviral therap*.ti,ab.
134. 'short-course-anti-retroviral therap*.ti,ab.
135. (combination adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
136. (combined adj (treatment* or therap* or regimen* or drug* or agent*)).ti,ab.
137. (monotherap* or mono-therap*).ti,ab.
138. 'dual therap*.ti,ab.
139. 'dual drug therap*.ti,ab.
140. bitherap*.ti,ab.
141. (PI or PIs or PI-based or PI-boosted or PI-containing or PI-therap* or PI-treatment* or PI-regimen*).ti,ab.

142. (Ritonavir-boosted or NRTI or NRTIs or NRTI-based).ti,ab.
143. 'protease inhibitor*.ti,ab.
144. (NRTI-containing or NRTI-therap* or NRTI-treatment* or NRTI-regimen*).ti,ab.
145. 'nucleoside reverse transcriptase inhibitor*.ti,ab.
146. 'nucleoside analog reverse transcriptase inhibitor*.ti,ab.
147. (NNRTI or NNRTIs or NNRTI-based or NNRTI-containing or NNRTI-therap* or NNRTI-treatment* or NNRTI-regimen*).ti,ab.
148. 'non nucleoside reverse transcriptase inhibitor*.ti,ab.
149. 'non-nucleoside reverse transcriptase inhibitor*.ti,ab.
150. 'nonnucleoside reverse transcriptase inhibitor*.ti,ab.
151. 'non nucleoside analog reverse transcriptase inhibitor*.ti,ab.
152. 'non-nucleoside analog reverse transcriptase inhibitor*.ti,ab.
153. 'nonnucleoside analog reverse transcriptase inhibitor*.ti,ab.
154. (NtRTI or NtRTIs or NtRTI-based or NtRTI-containing or NtRTI-therap* or NtRTI-treatment* or NtRTI-regimen*).ti,ab.
155. 'nucleotide reverse transcriptase inhibitor*.ti,ab.
156. 'nucleotide analog reverse transcriptase inhibitor*.ti,ab.
157. 'fusion inhibitor*.ti,ab.
158. 'CCR5 receptor antagonist*.ti,ab.
159. 'integrase inhibitor*.ti,ab.
160. 'maturation inhibitor*.ti,ab.
161. 'entry inhibitor*.ti,ab.
162. (Abacavir or ABC).tw.
163. Abacavir/
164. Abacavir plus lamivudine/
165. Abacavir plus lamivudine plus zidovudine/
166. (Didanosine or ddI).tw.
167. Didanosine/
168. (Emtricitabine or FTC).tw.
169. Emtricitabine/
170. Efavirenz plus emtricitabine plus tenofovir disoproxil/
171. Emtricitabine plus rilpivirine plus tenofovir disoproxil/
172. Emtricitabine plus tenofovir disoproxil/
173. (Lamivudine or 3TC).tw.
174. Lamivudine/
175. Efavirenz plus lamivudine plus zidovudine/
176. Lamivudine plus nevirapine plus stavudine/
177. Lamivudine plus nevirapine plus tenofovir disoproxil/
178. Lamivudine plus nevirapine plus zidovudine/
179. Lamivudine plus stavudine/
180. Lamivudine plus tenofovir disoproxil/
181. Lamivudine plus zidovudine/
182. (Stavudine or d4T).tw.
183. Stavudine/
184. (Tenofovir or TFV or TDF).tw.
185. Tenofovir/
186. Cobicistat plus elvitegravir plus emtricitabine plus tenofovir disoproxil/
187. Tenofovir disoproxil/
188. Tenofovir 3 hexadecyloxypropyl ester/
189. Tenofovir alafenamide/
190. (Zidovudine or AZT or ZDV).tw.
191. Zidovudine/
192. Zidovudine 5' phosphate/
193. Zidovudine 5' triphosphate/
194. Zidovudine derivative/
195. Zidovudine glucuronide/
196. (Delavirdine or DLV).tw.
197. Delavirdine/
198. (Efavirenz or EFV).tw.
199. Efavirenz/
200. (Etravirine or ETR).tw.
201. Etravirine/
202. (Nevirapine or NVP).tw.
203. Nevirapine/
204. (Rilpivirine or RPV).tw.
205. Rilpivirine/

206. (Atazanavir or ATV).tw.
 207. (Atazanavir adj Ritonavir).tw.
 208. (ATV adj r).tw.
 209. Atazanavir/
 210. Atazanavir plus ritonavir/
 211. (Darunavir or DRV).tw.
 212. (Darunavir adj Ritonavir).tw.
 213. (DRV adj r).tw.
 214. Darunavir/
 215. Darunavir plus ritonavir/
 216. (Fosamprenavir or FPV).tw.
 217. (Fosamprenavir adj Ritonavir).tw.
 218. (FPV adj r).tw.
 219. Fosamprenavir/
 220. Fosamprenavir plus ritonavir/
 221. (Indinavir or IDV).tw.
 222. (Indinavir adj Ritonavir).tw.
 223. (IDV adj r).tw.
 224. Indinavir/
 225. Indinavir plus ritonavir/
 226. (Lopinavir or LPV).tw.
 227. (Lopinavir adj Ritonavir).tw.
 228. (LPV adj r).tw.
 229. Lopinavir/
 230. Lopinavir plus ritonavir/
 231. (Nelfinavir or NFV).tw.
 232. (Nelfinavir adj Ritonavir).tw.
 233. (NFV adj r).tw.
 234. Nelfinavir/
 235. (Ritonavir or RTV).tw.
 236. Ritonavir/
 237. (Saquinavir or SQV).tw.
 238. (Saquinavir adj Ritonavir).tw.
 239. (SQV adj r).tw.
 240. Saquinavir/
 241. Ritonavir plus saquinavir/
 242. (Tipranavir or TPV).tw.
 243. (Tipranavir adj Ritonavir).tw.
 244. (TPV adj r).tw.
 245. Tipranavir/
 246. Ritonavir plus tipranavir/
 247. (Enfuvirtide or T-20).tw.
 248. Enfuvirtide/
 249. (Maraviroc or MVC).tw.
 250. Maraviroc/
 251. (Raltegravir or RAL).tw.
 252. Raltegravir/
 253. (Elvitegravir or EVG).tw.
 254. Elvitegravir/
 255. (Zalcitabine or ddC).tw.
 256. Zalcitabine/
 257. (Combivir or Trizivir or Kaletra or Epzicom or Kivexa or Truvada or Atripla).tw.
 258. 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223 or 224 or 225 or 226 or 227 or 228 or 229 or 230 or 231 or 232 or 233 or 234 or 235 or 236 or 237 or 238 or 239 or 240 or 241 or 242 or 243 or 244 or 245 or 246 or 247 or 248 or 249 or 250 or 251 or 252 or 253 or 254 or 255 or 256 or 257
 259. 105 or 258
 260. 54 and 259
 261. limit 260 to yr=1980-2013

Appendix 3.

Adapted Newcastle-Ottawa quality assessment checklist for cohort studies included in the systematic review.

A study can be awarded a maximum of one point (for items indicated with an asterisk) for each numbered criterion within the “Selection” and “Outcomes” categories. A maximum of two points can be given for “Comparability”.

Selection (maximum 4 points)

1) Representativeness of the exposed (HIV-positive women) cohort.

- a) Truly representative of the average pregnant female population in the community. *
- b) Somewhat representative of the average pregnant female in the community.
- c) Selected group of users e.g. nurses, volunteers, teenage mothers.
- d) No description of the derivation of the cohort.

2) Selection of the non-exposed (HIV-negative) cohort.

- a) The HIV-negative population is drawn from the same community as the HIV-positive population. *
- b) The HIV-negative population is drawn from a different source than the HIV-positive population.
- c) No description of the derivation of the HIV-negative population.

3) Ascertainment of exposure.

- a) HIV test conducted as part of the study. *
- b) HIV status confirmed from secure medical records (e.g. hospital records). *
- c) Structured interview-participant reported HIV-positive status.
- d) Written self-report.
- e) No description.

4) Demonstration that outcome of interest was not present at start of study.

- a) Yes. *
- b) No.

Comparability (maximum 2 points)

1) Comparability of cohorts on the basis of the analysis. In the analysis:

- a) Study controls for BMI, smoking, parity, and maternal age. *
- b) Study controls for any additional factor: prior history of adverse pregnancy outcome, maternal hypertension, anemia, illicit drug or alcohol use in pregnancy. *

Outcome (maximum 3 points)

1) Is the assessment of the outcome valid?

- a) Outcome was confirmed following clinical observation of outcome by clinician, midwife or trained birth attendant. *
- b) Medical records. *
- c) Self-report.
- d) No description.

2) Was gestational age accurately assessed?

- a) Yes, gestational age was determined according to early ultrasound (<14 weeks). *
- b) Gestational age was determined by: late ultrasound (≥14 weeks' gestation) or last normal menstrual period or neonatal assessment, e.g. Ballard score, or a combination of methods.
- c) Not reported or unspecified.

3) Adequacy of follow up of cohorts

- a) Complete follow up - all subjects accounted for. *
- b) Subjects lost to follow up unlikely to introduce bias - small number lost < 20 % follow up. *
- c) Follow up rate < 80% (lost to follow-up > 20%) and no description of those lost.
- d) No statement.

Appendix 4.

Adapted Newcastle-Ottawa quality assessment checklist for case-control studies included in the systematic review.

A study can be awarded a maximum of one point (for items indicated with an asterisk) for each numbered criterion within the “Selection” and “Exposure” categories. A maximum of two points can be given for “Comparability”.

Selection (maximum 5 points)

1) Is the case definition adequate?

- a) Yes, the cases are defined as women who experience one of the following perinatal outcomes: PTB, VPTB, PPROM, LBW, VLBW, term-LBW, preterm-LBW, SGA, VSGA, MC, SB, and NND (as defined by the systematic review protocol).*
- b) Yes, but definition is different to that which is specified in the HIV protocol.
- c) No description.

2) Representativeness of the cases.

- a) Consecutive or obviously representative series of cases.*
- b) Potential for selection biases or not stated.

3) Selection of controls.

- a) Community controls or hospital controls or matched control.*
- b) Control selected from a different population to the case.
- c) No description.

4) Definition of controls

- a) No history of the following perinatal outcome at delivery: PTB, VPTB, PPROM, LBW, VLBW, term-LBW, preterm-LBW, SGA, VSGA, MC, SB, and NND (as defined by the systematic review protocol).*
- b) Different definition to that which is specified in the HIV protocol or no description.

5) Was gestational age accurately assessed for cases and controls?

- a) Yes, gestational age was determined according to early ultrasound (<14 weeks). *
- b) Gestational age was determined by: late ultrasound or last normal menstrual period or clinically, e.g. Ballard score, or a combination of methods.
- c) Not reported or unspecified.

Comparability (maximum 2 points)

1) Comparability of cases and controls on the basis of the design or analysis

- a) Study controls for BMI, smoking, parity and maternal age. *
- b) Study controls for any additional factor: prior history of adverse pregnancy outcome, maternal hypertension, anemia, illicit drug or alcohol use in pregnancy. *

Exposure (maximum 3 points)

1) Is the assessment of exposure valid?

- a) An HIV test performed as part of the study. *
- b) Medical record of HIV status. *
- c) Interview blinded to case/control status.
- d) Interview not blinded to case/control status.
- e) Written self-report.
- f) No description.

2) Same method of ascertainment for cases and controls

- a) Yes. *
- b) No.

3) Non-response rate

- a) Same rate (not more than 5% difference) for both groups. *
- b) Non-respondents described.

Appendix 5.

Classification of studies included in systematic review, according to the adapted Newcastle-Ottawa quality assessment checklists.

Prospective and retrospective cohort studies	
Good quality	9 points – all requirements met.
Average quality	3 points in “selection” and 3 points in “outcome” sections.
	≥2 points in the “selection” and “outcome” sections, as well as ≥1 point in the “comparability” section.
Poor quality	< 2 points in the “selection” and/or “outcome” sections.
	2 points in the “selection” and “outcome” sections, but no points in the “comparability” section.
Case-control studies	
Good quality	10 points – all requirements met.
Average quality	4 points in the “selection” and 3 points in the “exposure” sections.
	≥3 points in the “selection” and ≥2 points in the “exposure” sections, as well as ≥1 point in the “comparability” section.
Poor quality	< 3 points in the “selection” and/or <2 points in the “exposure” sections.
	3 points in the “selection” and 2 points in the “exposure” sections, but no points in the “comparability” section.

Appendix 6.

Confounding factors adjusted for in individual studies.

Study	Matching	Risk factor analysis	Regression analysis (Multivariable analysis)
Adjorlolo et al 1991 ¹	-	-	-
Alger et al 1993 ²	-	Maternal age, parity, history of abortions, marital status, maternal weight	-
Ayisi et al 2003 ³	-	-	Maternal weight, maternal age, parity, education, ethnicity, season of delivery, hospitalization, sex of infant, hypertension, pre-eclampsia, polyhydramnios, abnormal presentation, POH (history of previous caesarean section, haemorrhage or repeated abortion)
Bergstrom et al 1995 ⁴	Maternal age and parity	-	-
Braddick et al 1990 ⁵	-	Maternal age, parity, smoking, STD	-
Bucceri et al 1997 ⁶	-	-	Maternal age, duration of IVDU, parity, smoking
Bulterys et al 1994 ⁷	-	BMI, mean body weight	Maternal age, parity, marital status, household income, education, smoking, STD
Coley et al 2001 ⁸	-	Education, marital status, height, weight, arm circumference, BMI	Maternal age, type of delivery, hypertension, smoking, maternal infection (malaria, tuberculosis), education, gravidity, height, occupation, marital status, arm circumference, STD
Ellis et al 2002 ⁹	-	-	Alcohol use, antenatal visits, hypertensive disorder, race, parity, maternal body weight, STD, diabetes, fetal distress
Ezeaka et al 2009 ¹⁰	Age and parity	Maternal height, social class, infant gender	-
Friis et al 2004 ¹¹	-	-	Maternal age, gravidity, season of birth, twin pregnancies, infant gender, malaria, arm fat area
Habib et al 2008 ¹²	-	-	Year of baby's birth, maternal residence, maternal occupation and paternal tribe
Halsey et al 1990 ¹³	-	-	-
Johnstone et al 1996 ¹⁴	Maternal age, parity, ethnic group, ANC, delivery in the same year, deprivation score and smoking	-	Maternal age, smoking, parity, deprivation score, anaemia, maternal weight at 20 weeks gestation
Kumar et al 1995 ¹⁵	Maternal age and parity	History of blood transfusion	-
Ladner et al 1998 ¹⁶	-	-	-
Lallemant et al 1989 ¹⁷	Maternal age, date of delivery, place of delivery	Occupation, marital status, POH, parity, gravidity, ANC visits, gestational age at first visit	-
Lepage et al 1991 ¹⁸	Maternal age and parity	Mothers occupation, fathers occupation, place of origin, income	Immunological status, maternal age, parity, twins
Leroy et al 1998 ¹⁹	Maternal age and parity	Marital status, occupation, gestational age at enrollment, pregnancy complications	Maternal age, parity, STD, anaemia, malaria, education, prematurity

Markson et al 1996 ²⁰	Location	Maternal age, education, ANC visits, year of delivery	Illicit drug use, race, maternal age, education, year of delivery, location, smoking, medicaid enrolment, antenatal visits
Maynard et al 1990 ²¹	-	-	-
Mitgitti et al 2008 ²²	-	Parity, ethnicity, location of ANC, gestational age at delivery	Infant gender, maternal age, gestational age at delivery, antenatal visits
Mmiro et al 1993 ²³	-	Marital status and transfusion	-
Musana et al 2009 ²⁴	Maternal age and gestational age	Marital status, employment, gestational age at enrollment, hospitalization, mode of delivery, hypertension, chorioamnionitis, meconium staining in liquor	-
Mwanyumba et al 2001 ²⁵	-	-	Maternal age, parity, sex of infant, religion, STD, anaemia, POH, hypertension, illicit drug use, smoking
Ndirangu et al 2012 ²⁶	-	MUAC, place of delivery, mode of delivery, height, BMI	Infant gender, location, water-source, toilet type, delivery place, parity, maternal age, education, weight, height and MUAC
Noble et al 2005 ²⁷	-	Parity, occupation, residence, history of STD, infant gender	Maternal age, gravidity, education, marital status, BMI, iron supplementation
Rollins et al 2007 ²⁸	-	-	Maternal age, maternal residence, education, infant gender, MUAC
Ryder et al 1989 ²⁹	Maternal age and parity	-	-
Selwyn et al 1989 ³⁰	-	-	-
Sutton et al 1999 ³¹	-	-	Maternal age, parity, malaria, trichomoniasis, chorioamnionitis, SES
Taha et al 1995 ³²	-	-	-
Temmerman et al 1994 ³³	Maternal age and parity	Marital status, education, history of blood transfusion, history of oral contraception, POH, mode of delivery	-
Ticconi et al 2003 ³⁴	-	-	Maternal age, parity, malaria, HIV treatment, malaria treatment
Van den Broek et al 2014 ³⁵	-	Maternal age, parity, POH, BMI	Maternal age, BMI, weight gain, anaemia, malaria
ANC = antenatal care, BMI = body mass index, HIV = Human Immunodeficiency Virus, IVU = Intravenous Drug Use, MUAC = mid-upper arm circumference, POH = past obstetric history, SES = socio-economic status, STD = sexually transmitted disease.			

Appendix 7

Combinations of methods used to determine gestational age (mixed-methods) in studies included in systematic review.

Method of gestational age determination	Number of studies
Late ultrasound and LNMP	2
Late ultrasound and neonatal assessment (Ballard score)	1
Late ultrasound and neonatal assessment (Finnström score)	1
LNMP and neonatal assessment (Ballard score)	5
LNMP and SFH	1
Late ultrasound, LNMP and neonatal assessment (type not specified)	1
LNMP, neonatal assessment (Dubowitz score) and SFH	1
LNMP = last normal menstrual period. SFH = symphysio-fundal height. Late ultrasound = ultrasound ≥ 14 weeks' gestation.	

Appendix 8.

Quality assessment scores of studies included in systematic review, according to the adapted Newcastle-Ottawa quality assessment checklists.

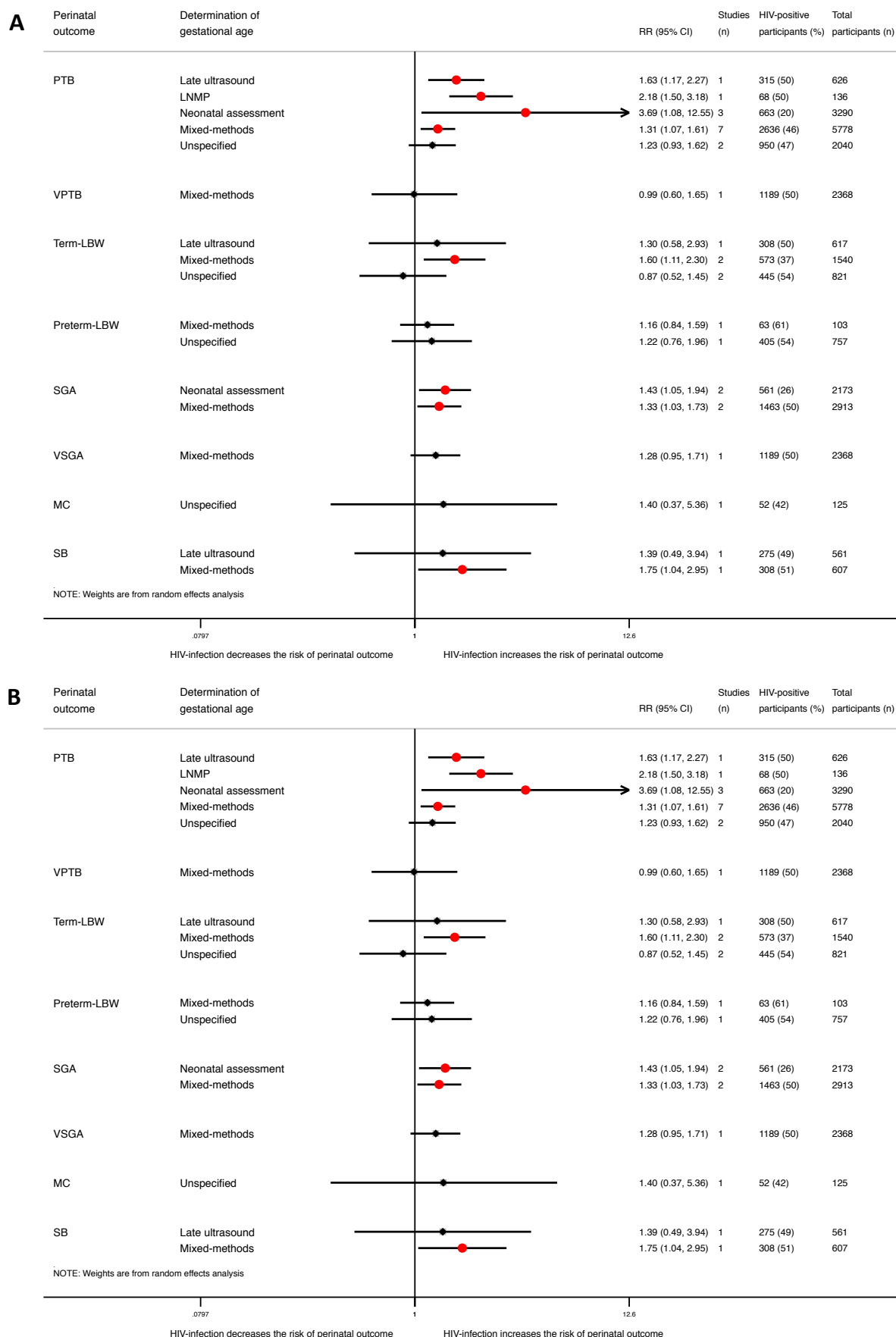
Study	Quality assessment			
	Selection (maximum 4 points) [Case-control study (cc): maximum 5 points]	Comparability (maximum 2 points)	Outcome/exposure (maximum 3 points)	Overall quality assessment (Good/Average/Poor)
Sub-Saharan Africa				
Adjorlolo et al 1991 ¹	★★★	-	-	Poor
Ayisi et al 2003 ³	★★★	★★	★★	Average
Bergstrom et al 1995 ⁴ (cc)	★★★	★	★★★	Average
Braddick et al 1990 ⁵	★★★★	★★	★★	Average
Bulterys et al 1994 ⁷	★★★★	★	★★	Average
Coley et al 2001 ⁸	★★★★	★★	★★	Average
Ezeaka et al 2009 ¹⁰	★★★★	★★	★★	Average
Friis et al 2004 ¹¹	★★★★	★	★	Poor
Habib et al 2008 ¹²	★★★	-	★	Poor
Ladner et al 1998 ¹⁶	★★★★	-	★★	Poor
Lallemant et al 1989 ¹⁷	★★★★	★★	★★	Average
Lepage et al 1991 ¹⁸	★★★	★	★★	Average
Leroy et al 1998 ¹⁹	★★★★	★★	★★	Average
Mmiro et al 1993 ²³	★★★★	-	★★	Poor
Musana et al 2009 ²⁴	★★★	★★	★★	Average
Mwanyumba et al 2001 ²⁵	★★★	★★	★	Poor
Ndirangu et al 2012 ²⁶	★★★★	★	★	Poor
Noble et al 2005 (cc) ²⁷	★★★★	★★	★★★	Average
Rollins et al 2007 ²⁸	★★★★	★	★★	Average
Ryder et al 1989 ²⁹	★★★★	★★	★★	Average
Sutton et al 1999 ³¹	★★★	★	★★	Average
Taha et al 1995 ³²	★★★	-	★★	Poor
Temmerman et al 1994 ³³	★★★★	★★	★	Poor
Ticconi et al 2003 ³⁴	★★	★	★	Poor
Van den Broek et al 2014 (cc) ³⁵	★★★★	★★	★★	Average
Europe				
Bucceri et al 1997 ⁶	★★★	★★	★★	Average
Johnstone et al 1996 ¹⁴	★★	★★	★	Poor
The Americas and Caribbean				
Alger et al 1993 ²	★★★★	★★	★★	Average
Ellis et al 2002 ⁹	★★★	★★	★	Poor

Halsey et al 1990 ¹³	★★★★★	★	★★	Average
Markson et al 1996 ²⁰	★★★	★★	★	Poor
Maynard et al 1990 ²¹	★★	★	★★	Average
Selwyn et al 1989 ³⁰	★★★	★	★	Poor
Asia				
Kumar et al 1995 ¹⁵	★★★★★	★	★★	Average
Mitgitti et al 2008 ²²	★★★	★	★	Poor

Appendix 9.

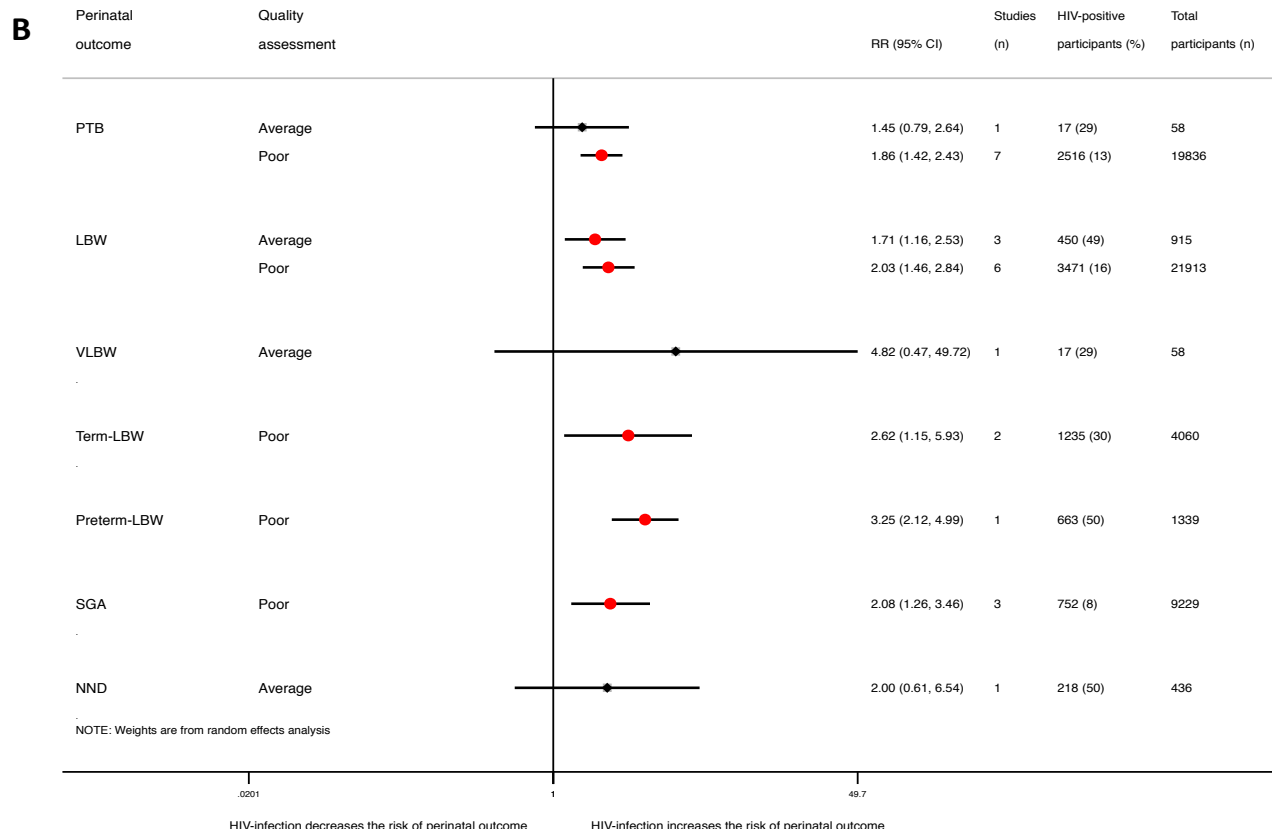
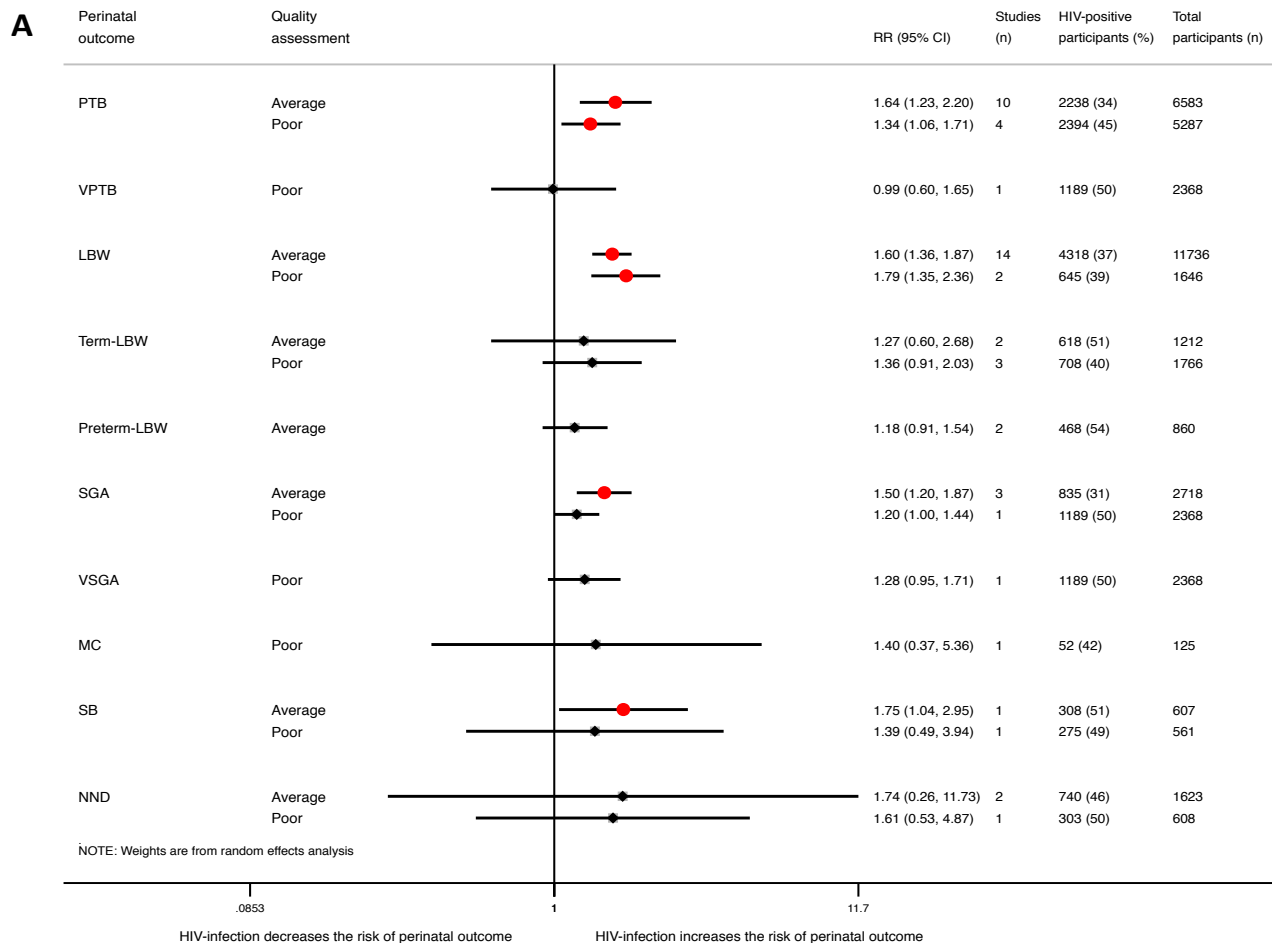
Case-control studies assessing the association between ART-naïve maternal HIV-infection and perinatal outcomes.

Study ID	Outcome	OR (95% CI)	HIV-positive women in cases	HIV-positive women in controls
Bergstrom et al 1995 ⁴	LBW	0.32 (0.01-8.38)	0/51	1/51
Noble et al 2005 ²⁷	PTB	0.81 (0.43-1.52)	15/53	144/440
Van Den Broek et al 2014 ³⁵	PTB	1.15 (0.89-1.49)	99/351	439/1729
OR (95% CI) = = odds ratio with 95% confidence interval. LBW = low birthweight. PTB = preterm birth.				



Appendix 10. Perinatal outcomes associated with ART-naïve maternal HIV infection, by method used to determine gestational age. A: Prospective cohort studies, B: Retrospective cohort studies.

Summary forest plot displaying the random-effects meta-analysis results of the association between ART-naïve maternal HIV-infection and perinatal outcomes, stratified according to the method used to determine gestational age in each study. Statistically significant effects are presented in red. RR (95%CI) = relative risk with 95% confidence interval, n = number, % = number of HIV-positive participants as a proportion of the total number of participants in the included studies (for each outcome and study design). PTB = preterm birth, VPTB = very preterm birth, LBW = low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age, MC = miscarriage, SB = stillbirth, LNMP = last normal menstrual period. For details of mixed-methods refer to appendix 7.



Appendix 11. Perinatal outcomes associated with ART-naïve maternal HIV infection, by adapted Newcastle-Ottawa quality assessment of studies. A: Prospective cohort studies, B: Retrospective cohort studies.

Summary forest plot displaying the random-effects meta-analysis results of the association between ART-naïve maternal HIV-infection and perinatal outcomes, stratified according to the overall quality assessment of each study. Statistically significant effects presented in red. RR (95%CI) = relative risk with 95% confidence interval, n = number, % = number of HIV-positive participants as a proportion of the total number of participants in the included studies (for each outcome and study design). PTB = preterm birth, VPTB = very preterm birth, LBW = low birthweight, VLBW = very low birthweight, SGA = small-for-gestational-age, VSGA = very small-for-gestational-age, MC = miscarriage, SB = stillbirth, NND = neonatal death.

References

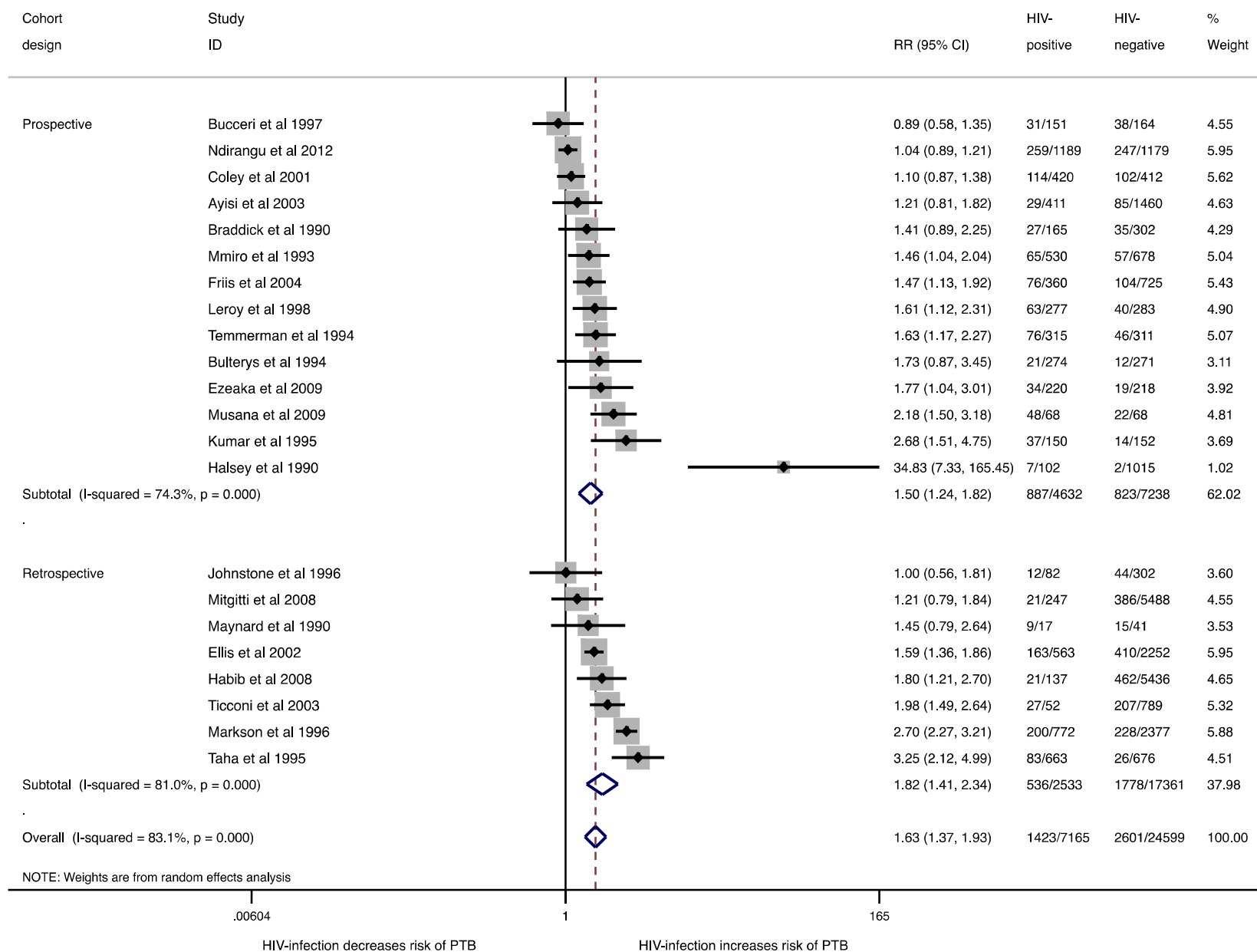
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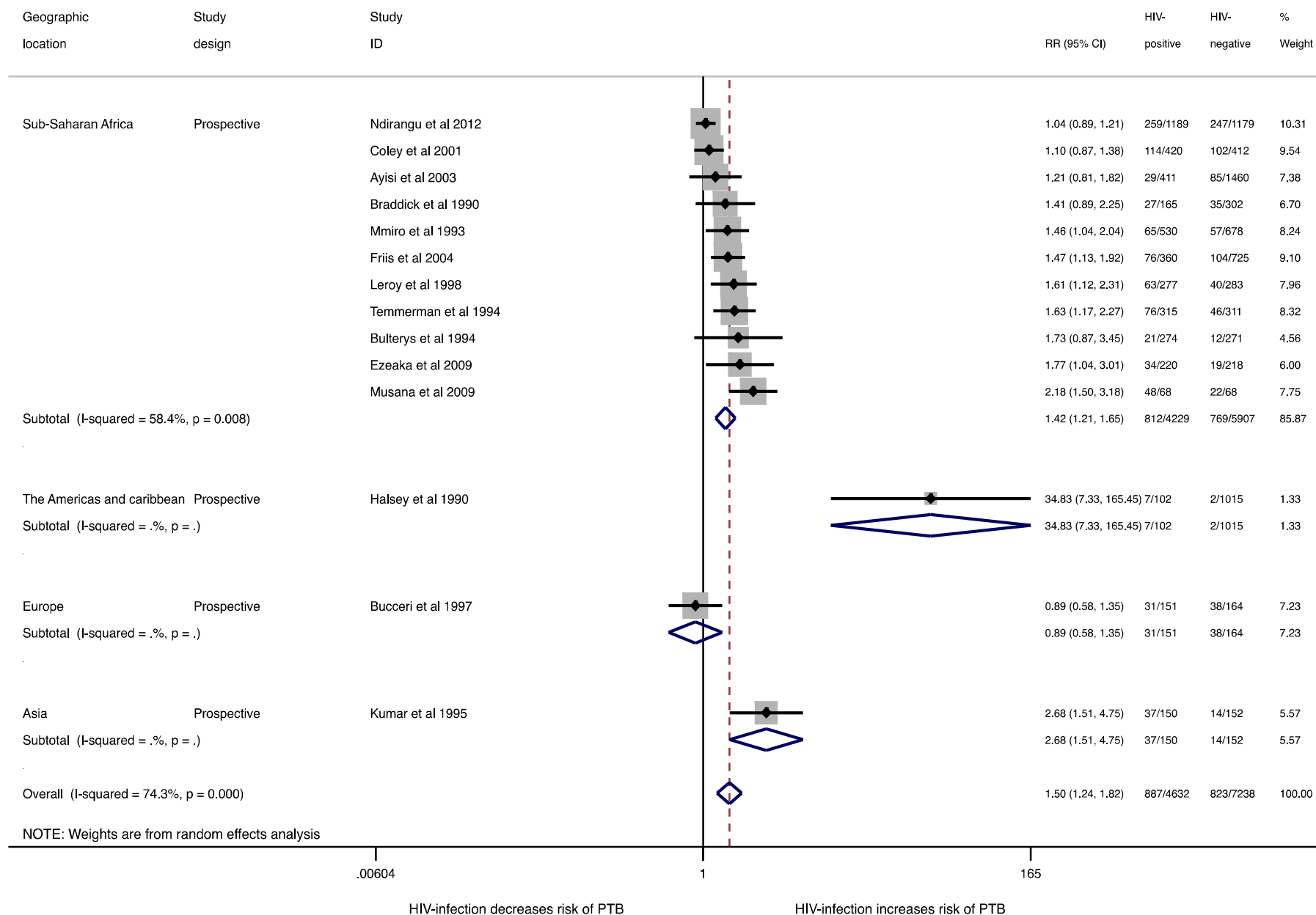
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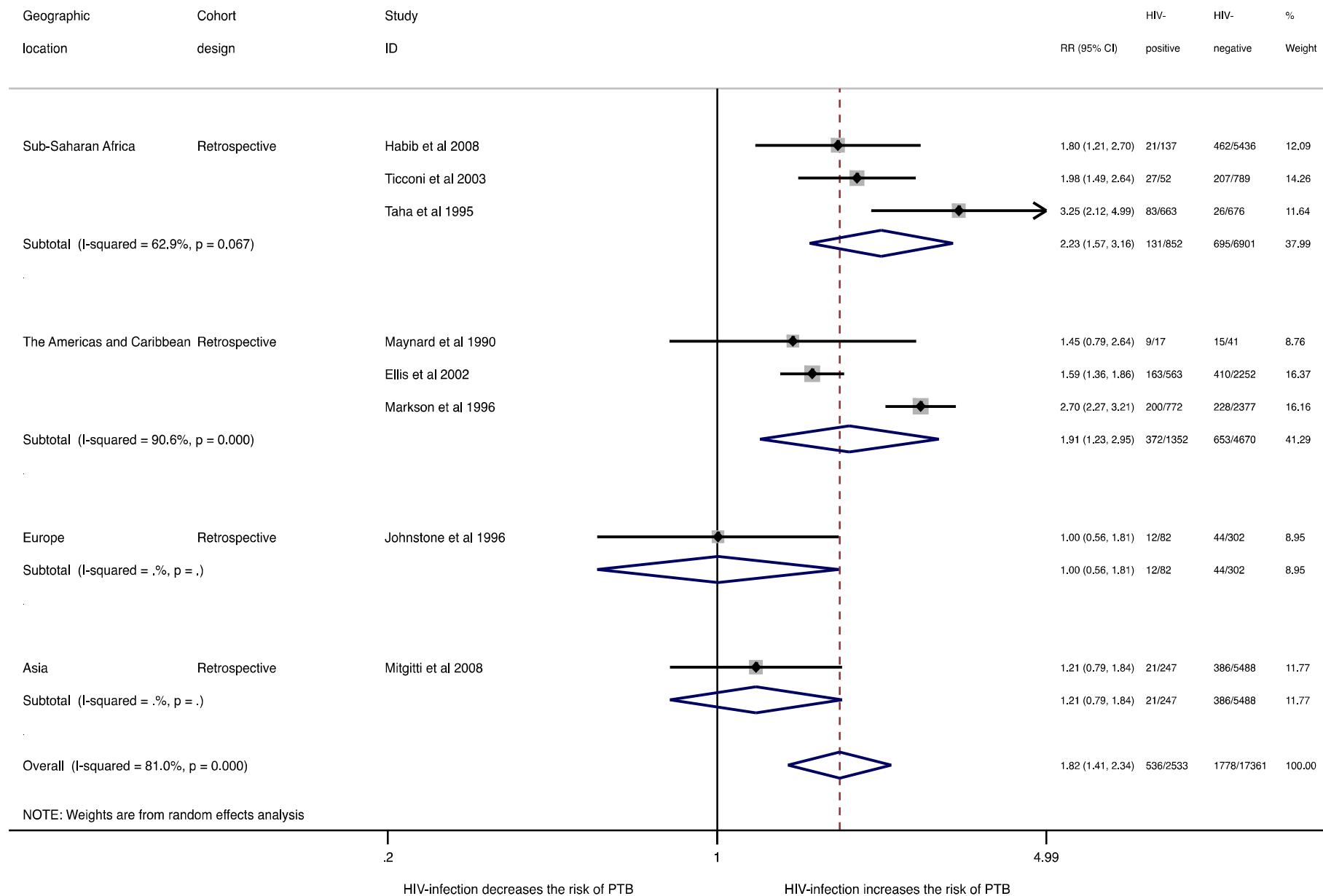
Systematic review and meta-analysis of perinatal outcomes associated with maternal HIV-infection.

Appendix 13.

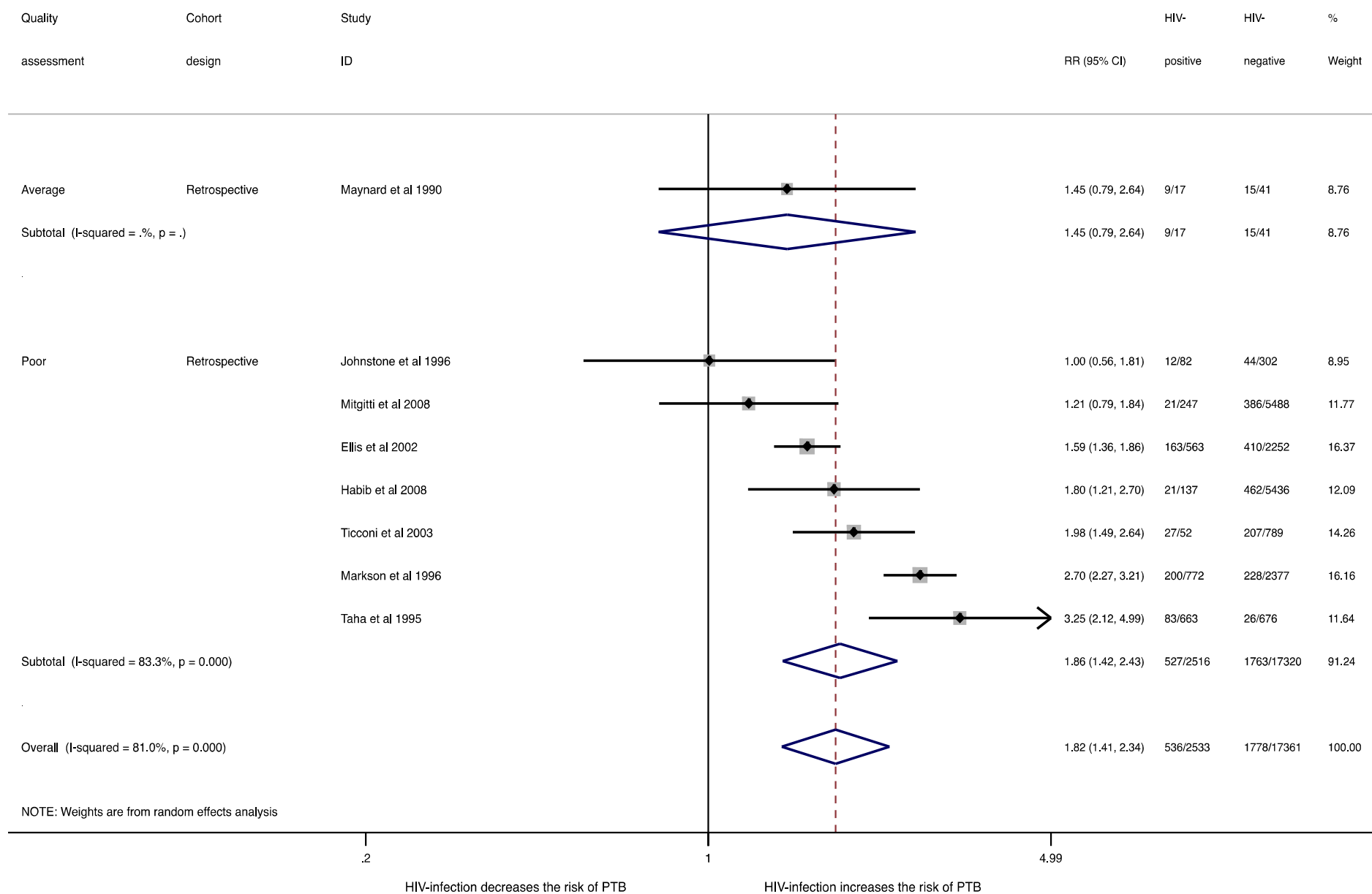


Appendix 13·1: PTB associated with ART-naïve maternal HIV-infection, by study design.

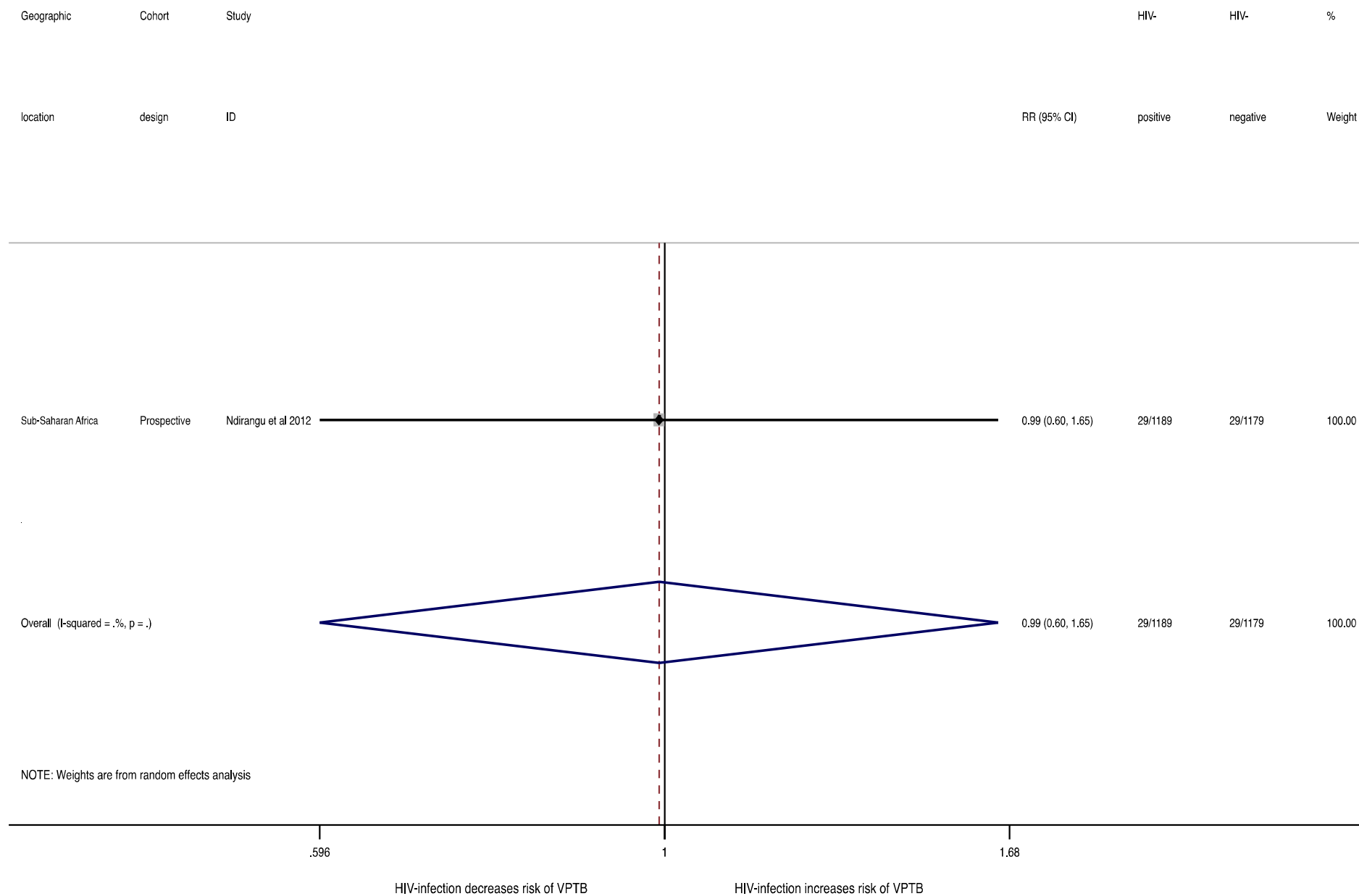




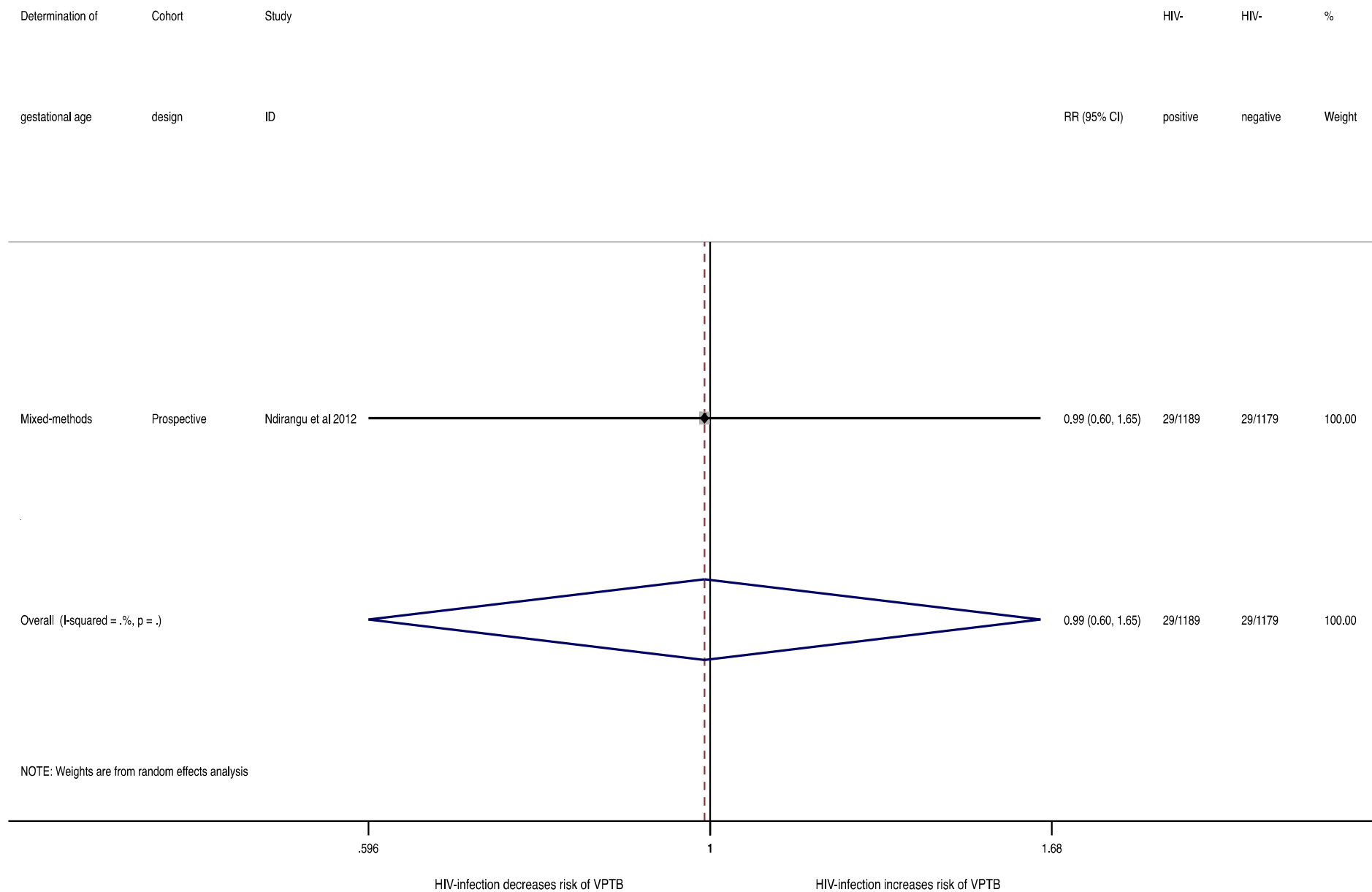
Appendix 13·3: PTB associated with ART-naïve maternal HIV-infection, by geographic region: retrospective studies.



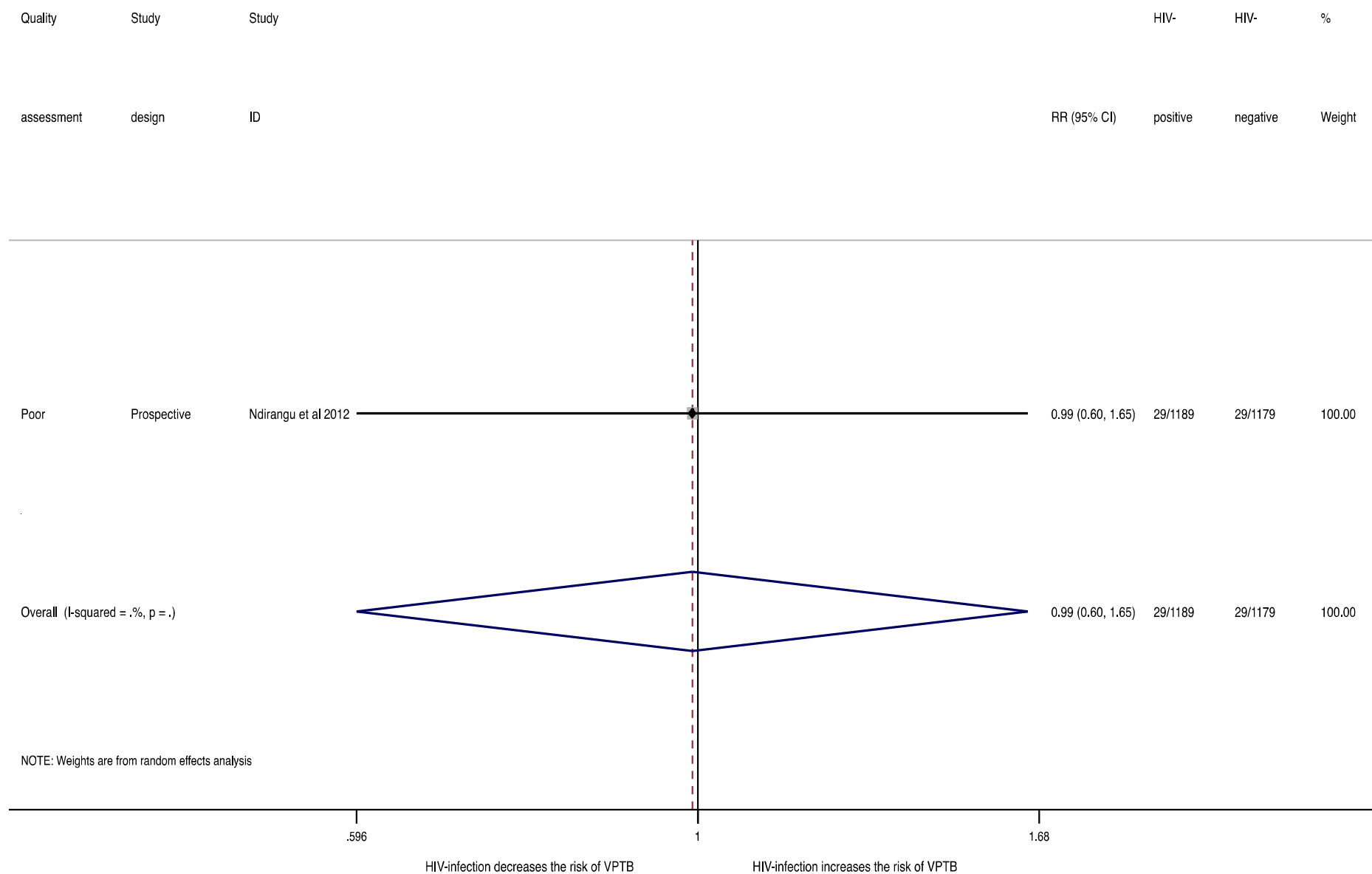
Appendix 13·7: PTB associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective studies.



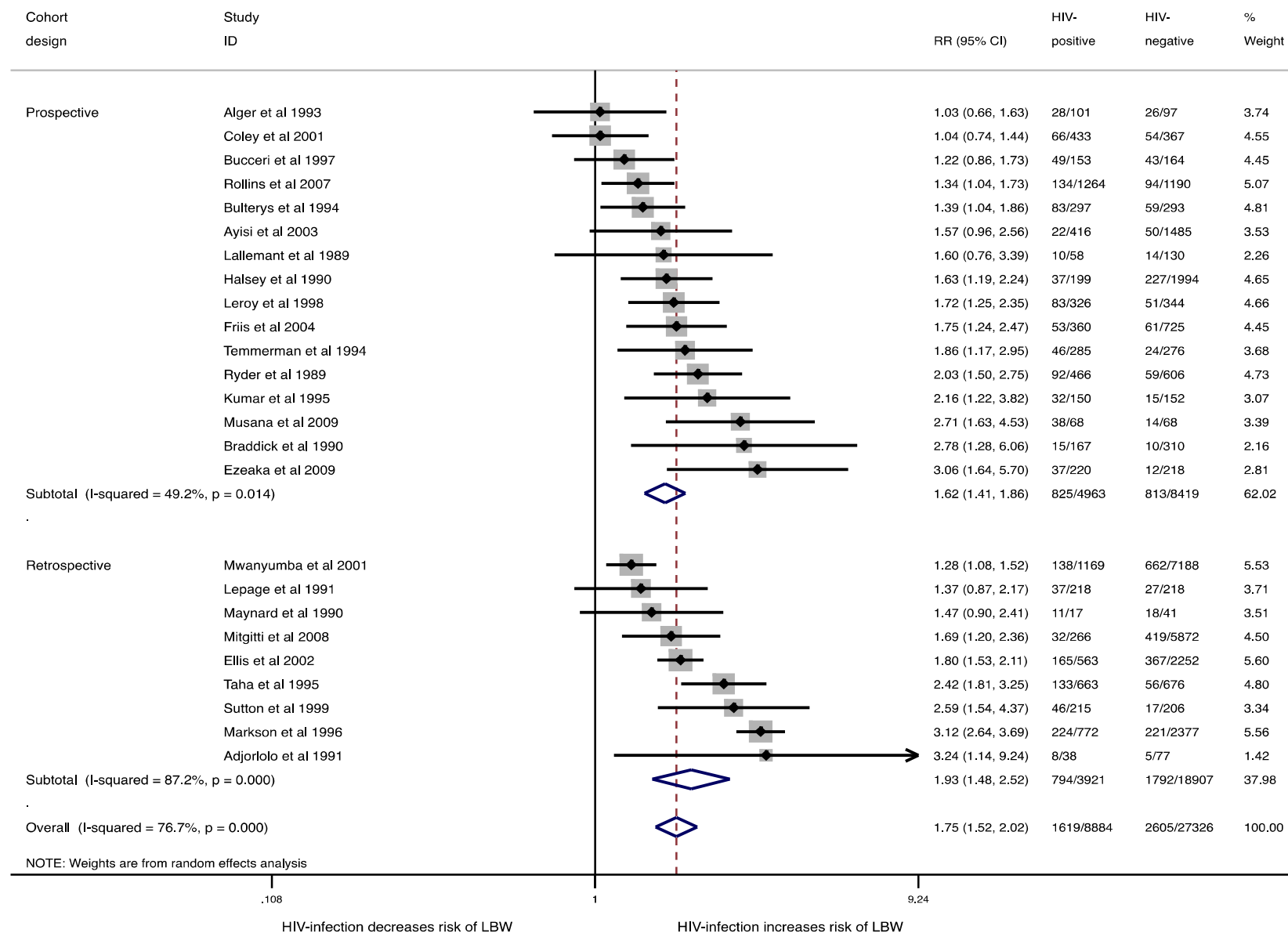
Appendix 13·9: VPTB associated with ART-naïve maternal HIV-infection, by geographic region: prospective study.



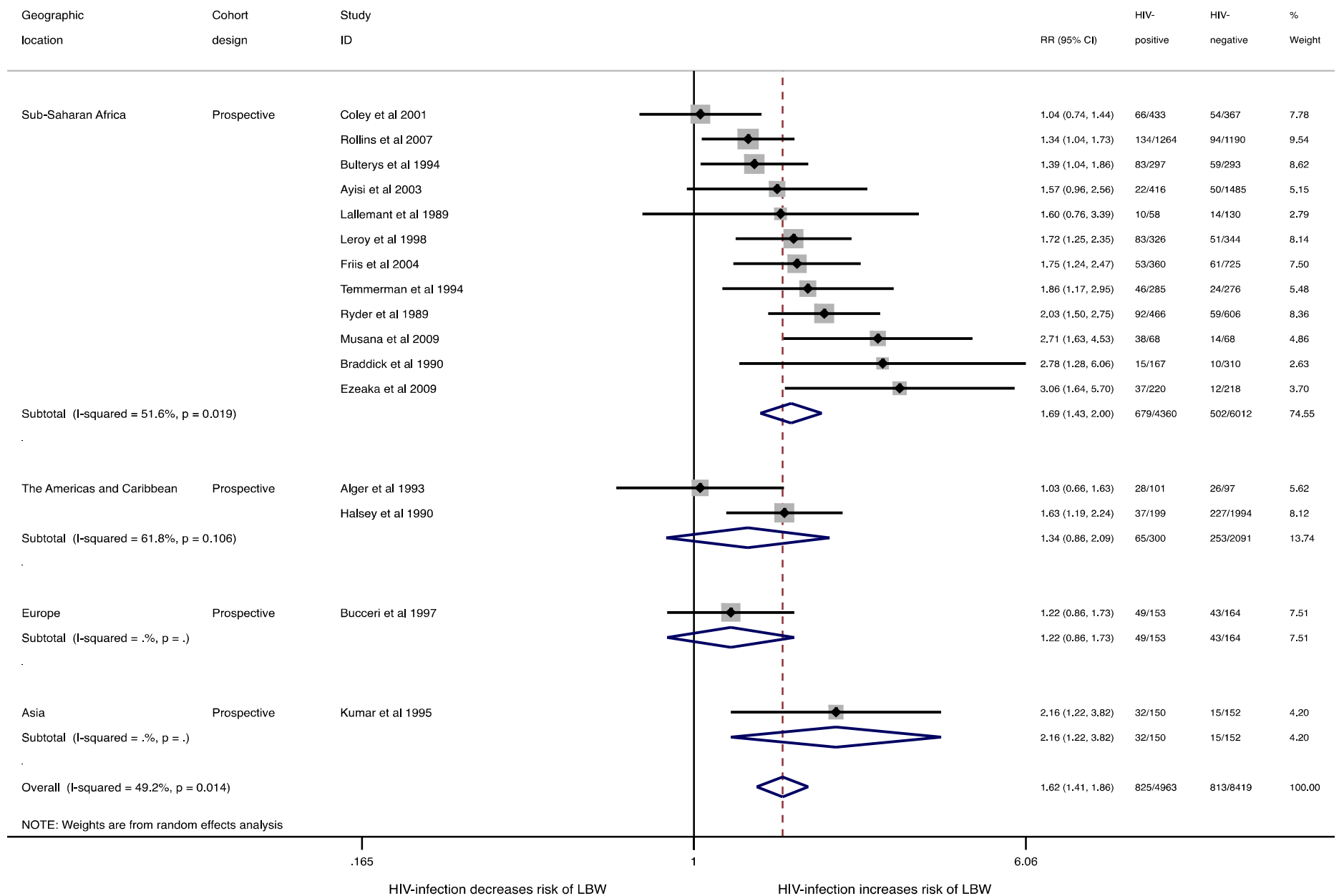
Appendix 13·10: VPTB associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: prospective study.



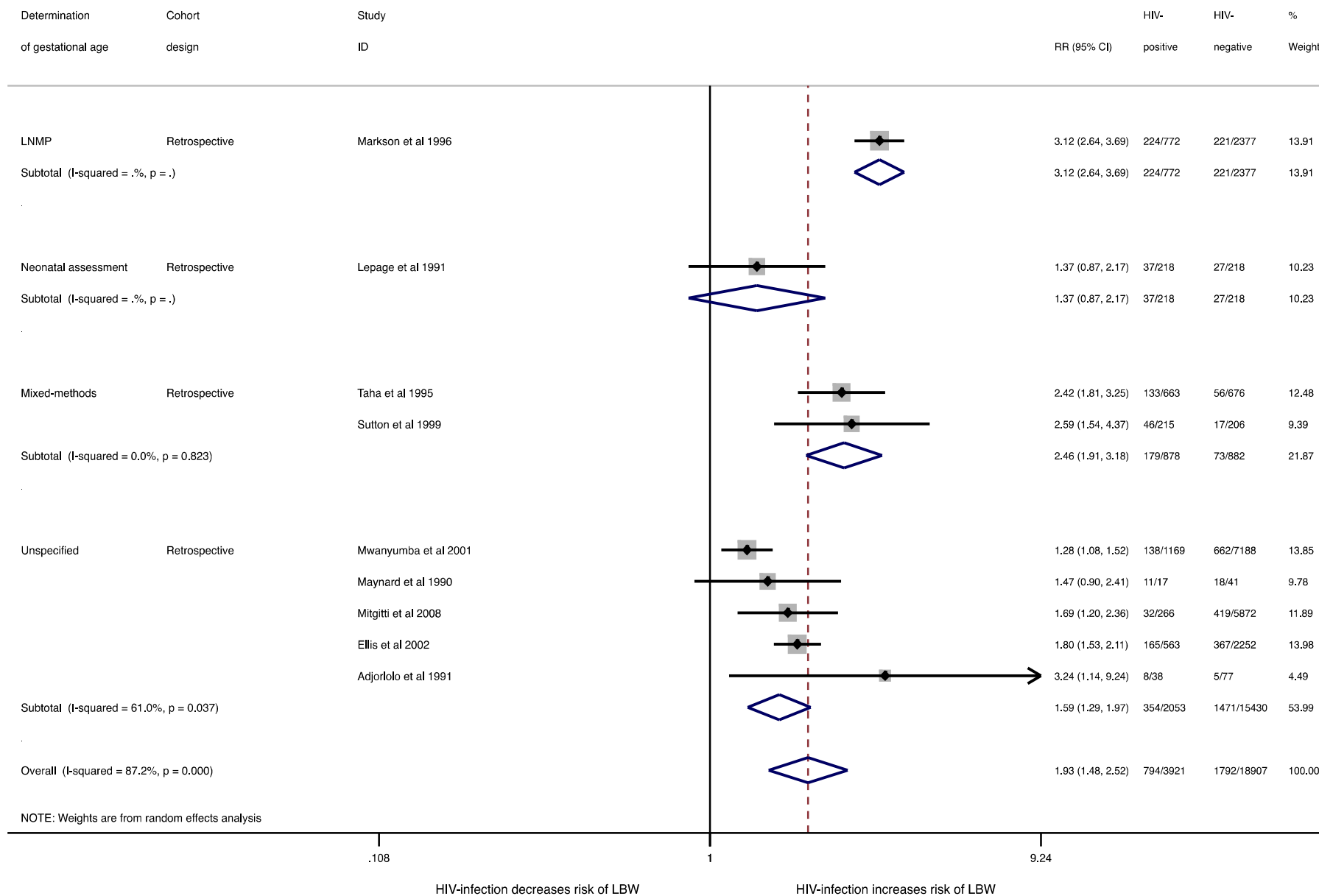
Appendix 13-11: VPTB associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective study.



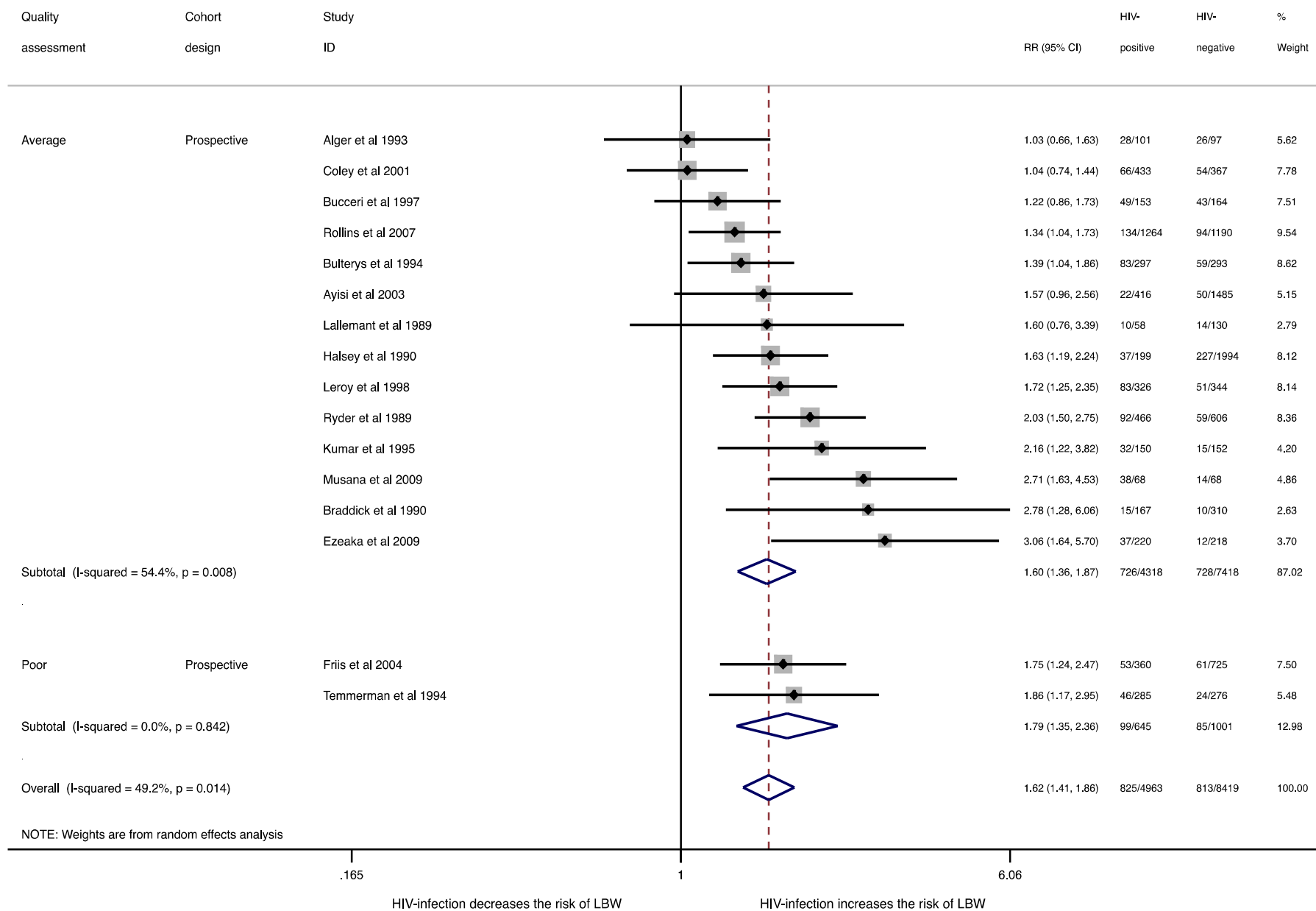
Appendix 13·12: LBW associated with ART-naïve maternal HIV-infection, by study design.



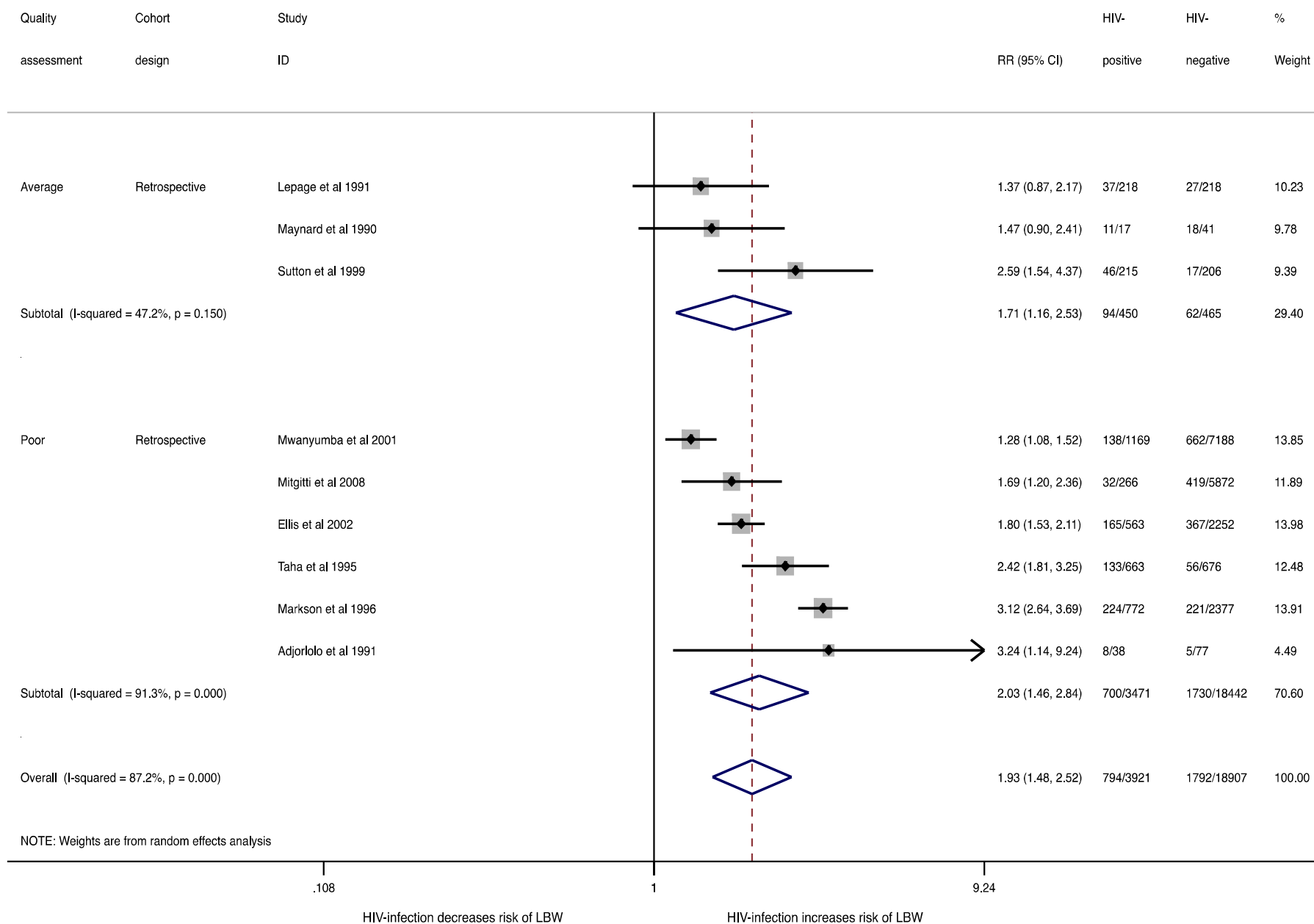
Appendix 13·13: LBW associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.



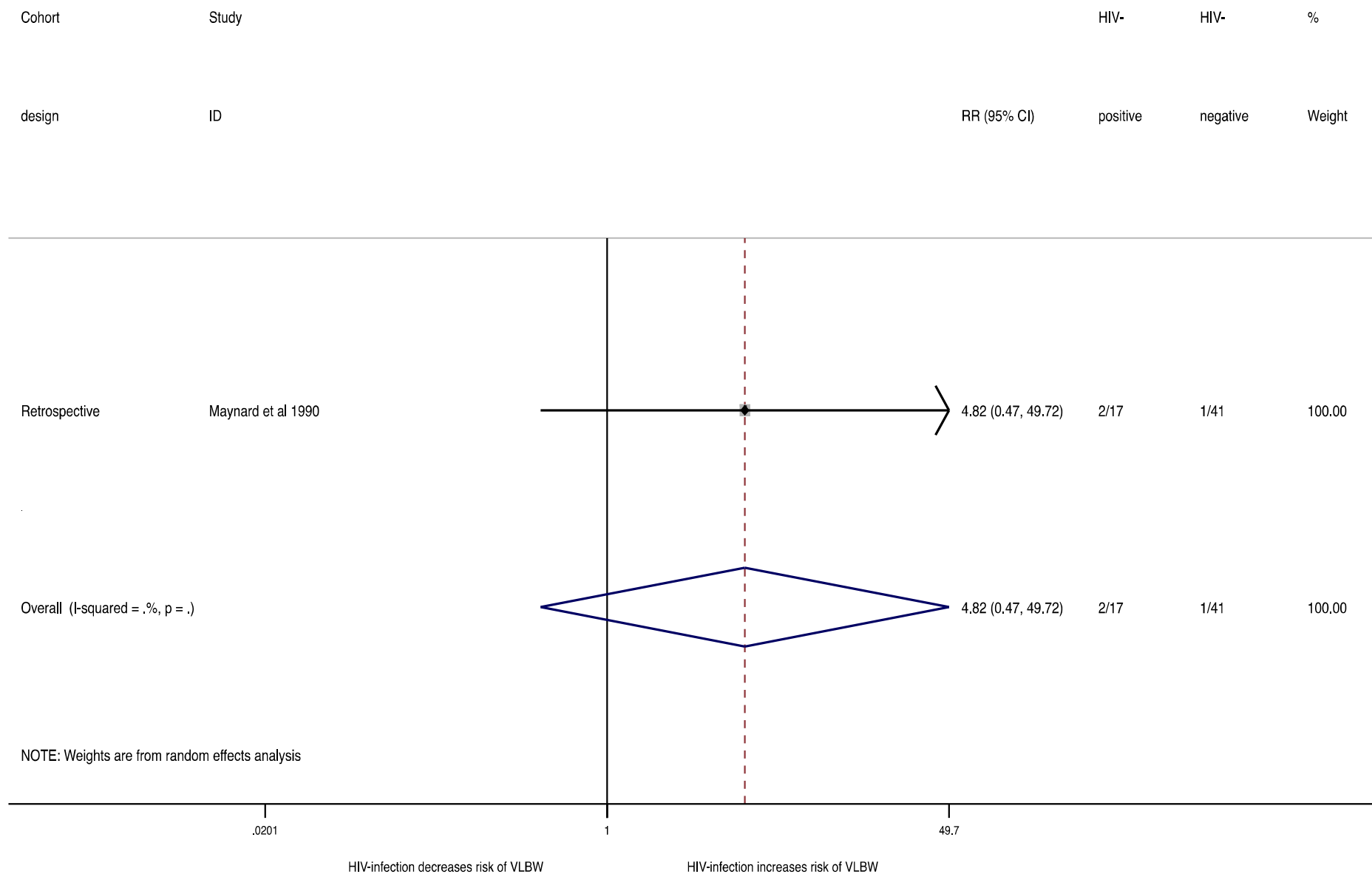
Appendix 13·16: LBW associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: retrospective studies.



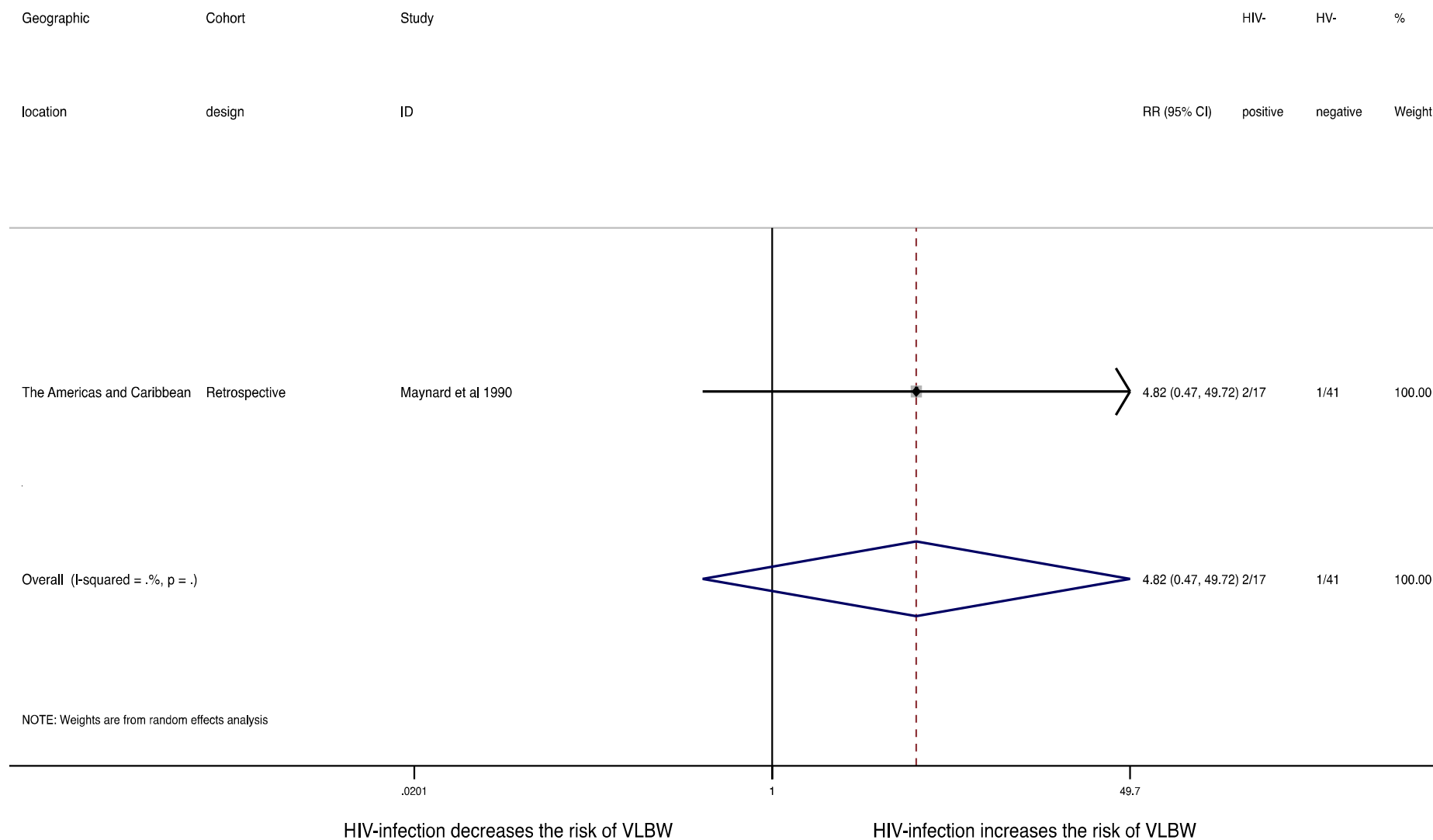
Appendix 13·17: LBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective studies.



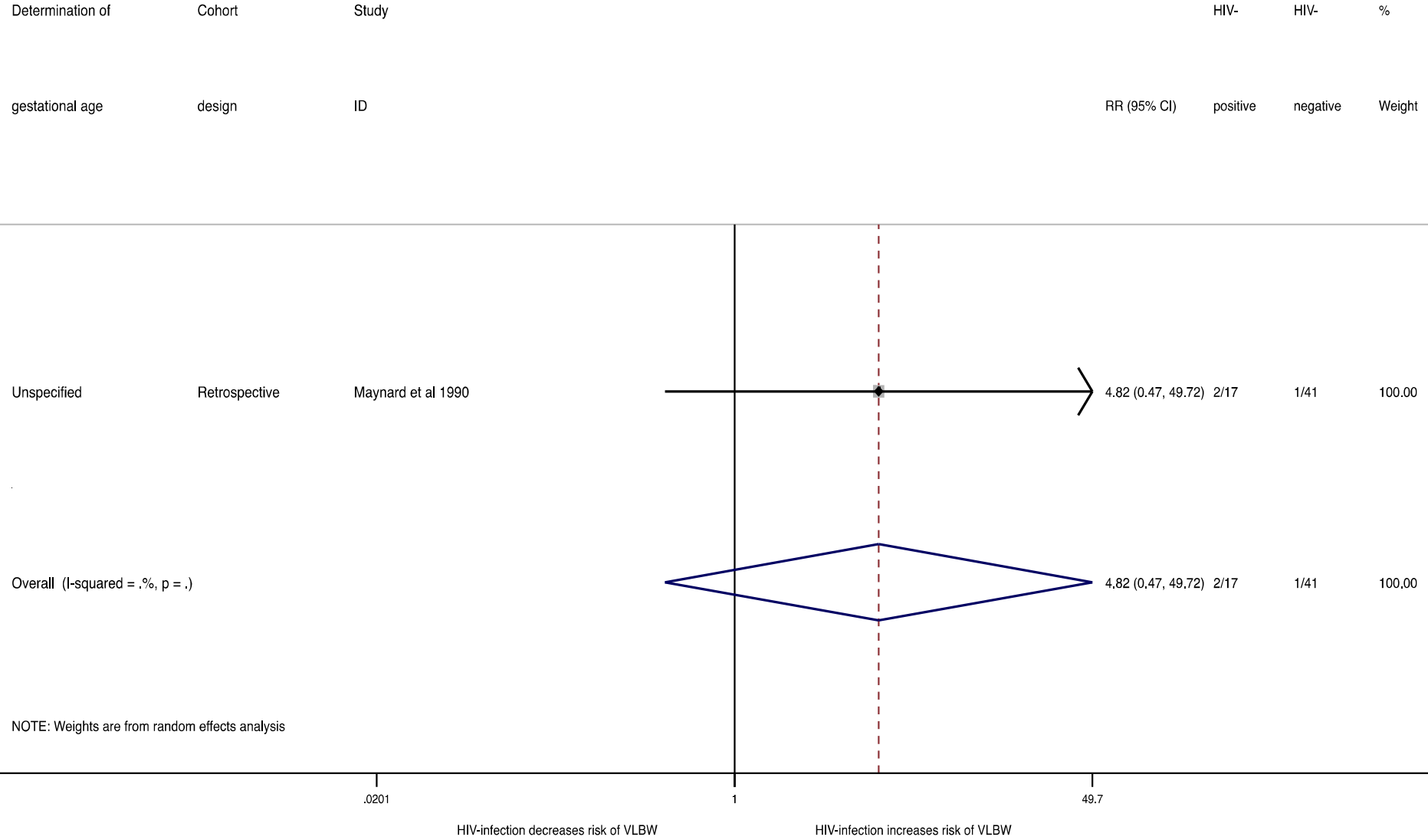
Appendix 13-18: LBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective studies.



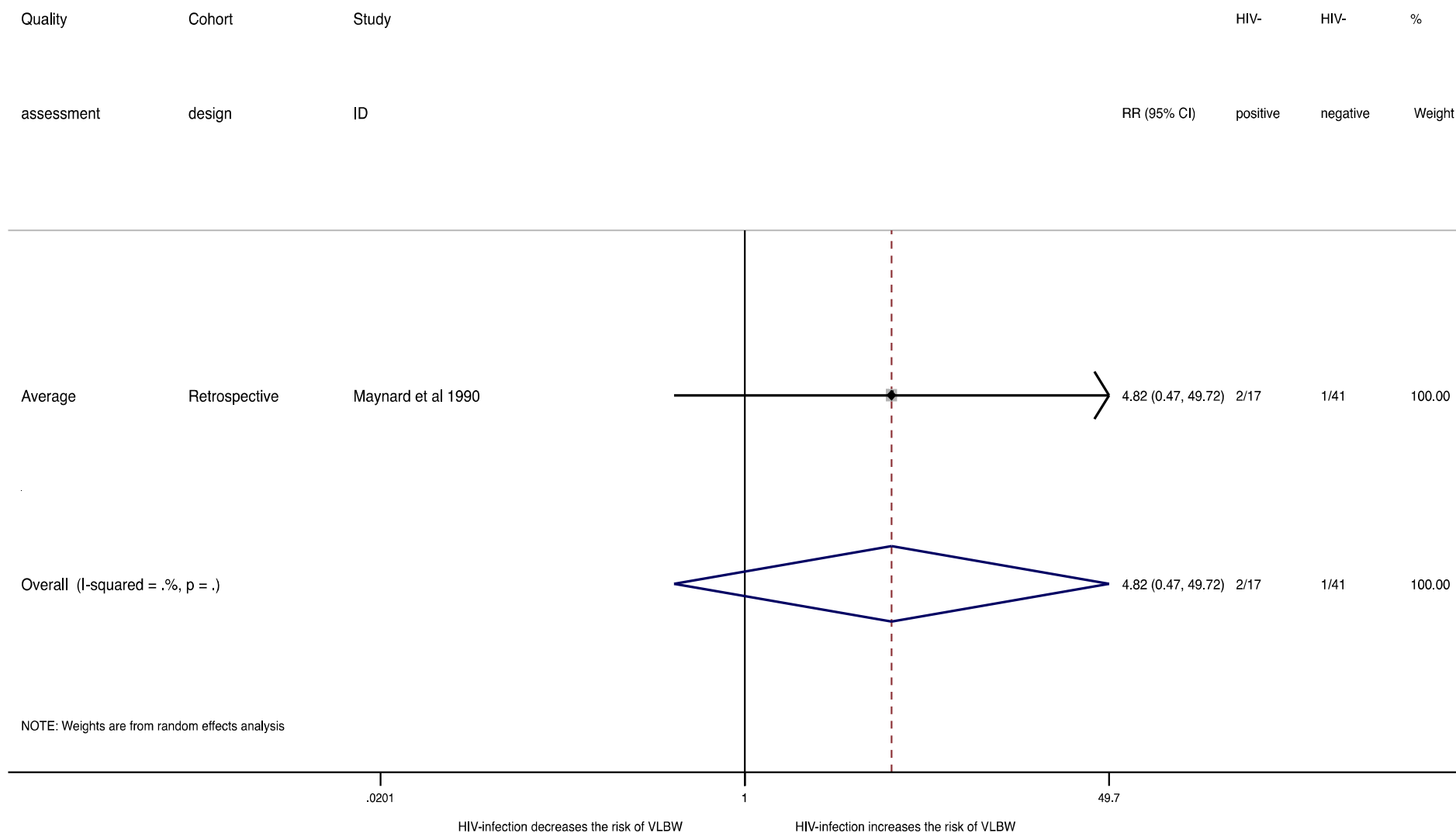
Appendix 13·19: VLBW associated with ART-naïve maternal HIV-infection, by study design.



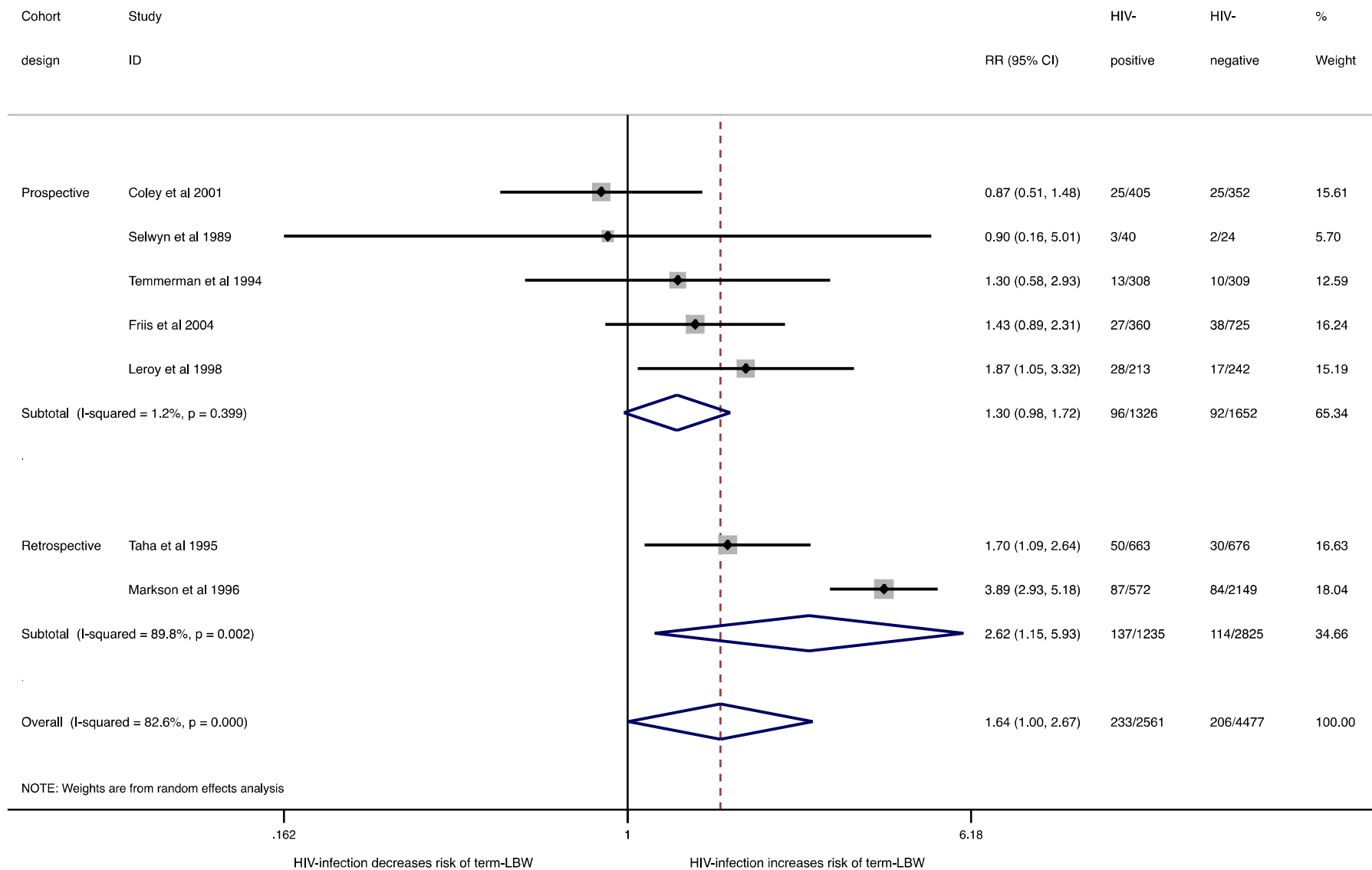
Appendix 13:20: VLBW associated with ART-naïve maternal HIV-infection, by geographic region: retrospective study.



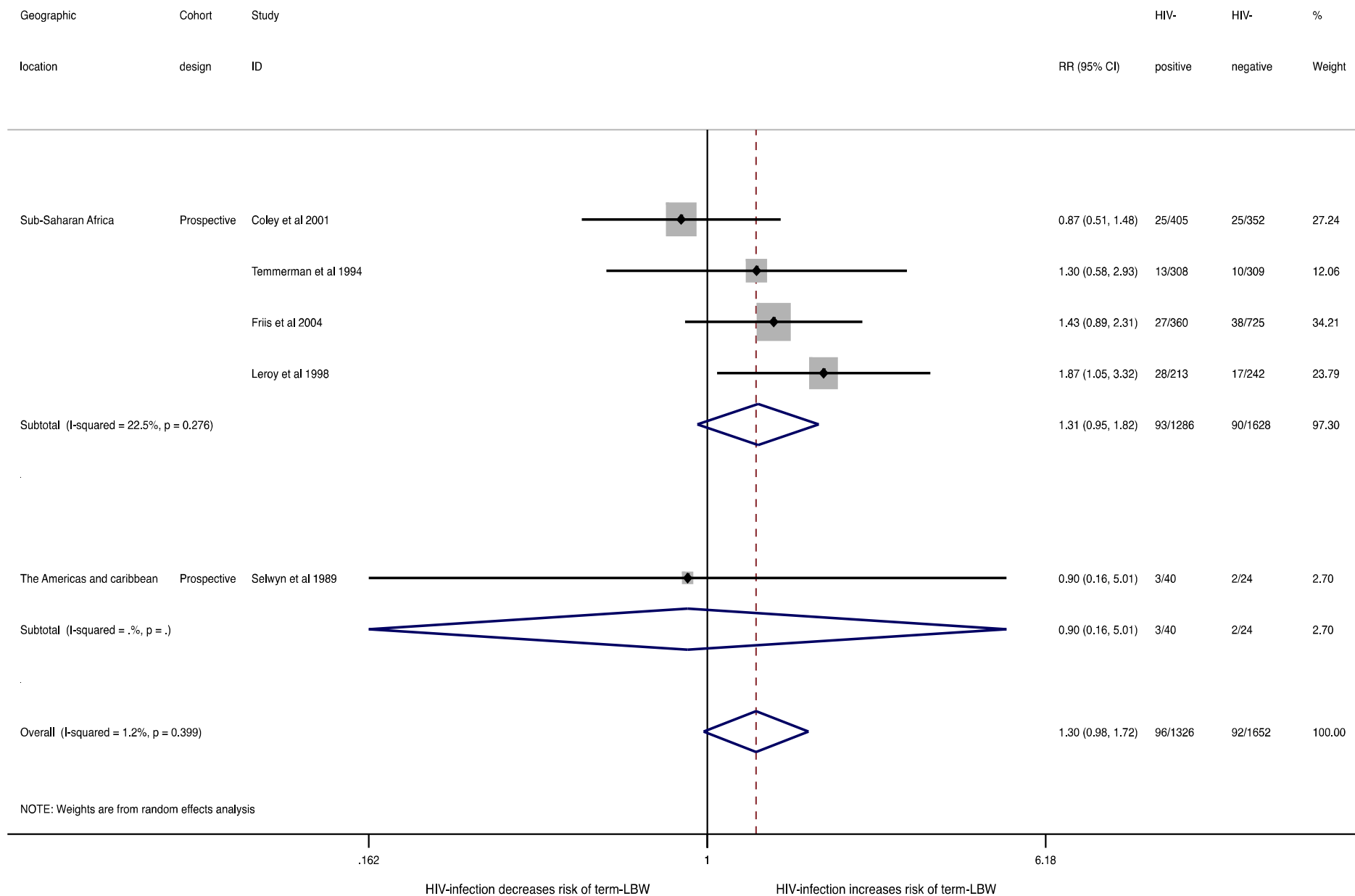
Appendix 13·21: VLBW associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: retrospective study.



Appendix 13-22: VLBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective study.



Appendix 13-23: Term-LBW associated with ART-naïve maternal HIV-infection, by study design.



Appendix 13·24: Term-LBW associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.

Geographic location	Cohort design	Study ID	RR (95% CI)	HIV- positive	HIV- negative	% Weight
Sub-Saharan Africa	Retrospective	Taha et al 1995	1.70 (1.09, 2.64)	50/663	30/676	47.92
Subtotal (I-squared = .%, p = .)			1.70 (1.09, 2.64)	50/663	30/676	47.92
The Americas and Caribbean	Retrospective	Markson et al 1996	3.89 (2.93, 5.18)	87/572	84/2149	52.08
Subtotal (I-squared = .%, p = .)			3.89 (2.93, 5.18)	87/572	84/2149	52.08
Overall (I-squared = 89.8%, p = 0.002)			2.62 (1.15, 5.93)	137/1235	114/2825	100.00

NOTE: Weights are from random effects analysis

HIV-infection decreases the risk of term-LBW HIV-infection increases the risk of term-LBW

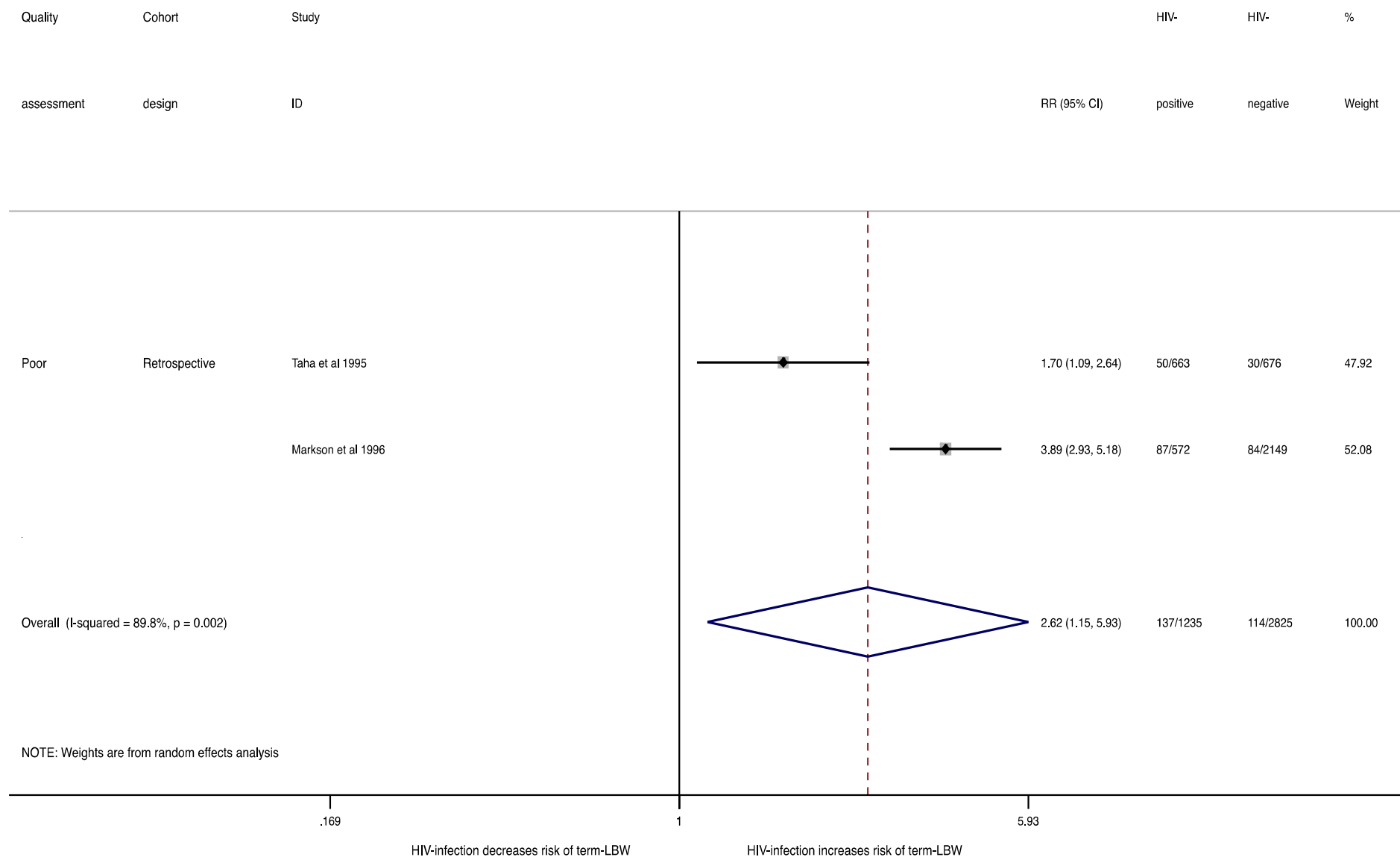
Appendix 13-25: Term-LBW associated with ART-naïve maternal HIV-infection, by geographic region: retrospective studies.

Quality	Cohort	Study	RR (95% CI)	HIV- positive	HIV- negative	%
assessment	design	ID				Weight
Average	Prospective	Coley et al 2001	0.87 (0.51, 1.48)	25/405	25/352	27.24
		Leroy et al 1998	1.87 (1.05, 3.32)	28/213	17/242	23.79
Subtotal	(I-squared = 72.7%, p = 0.056)		1.27 (0.60, 2.68)	53/618	42/594	51.03
Poor	Prospective	Selwyn et al 1989	0.90 (0.16, 5.01)	3/40	2/24	2.70
		Temmerman et al 1994	1.30 (0.58, 2.93)	13/308	10/309	12.06
		Friis et al 2004	1.43 (0.89, 2.31)	27/360	38/725	34.21
Subtotal	(I-squared = 0.0%, p = 0.871)		1.36 (0.91, 2.03)	43/708	50/1058	48.97
Overall	(I-squared = 1.2%, p = 0.399)		1.30 (0.98, 1.72)	96/1326	92/1652	100.00

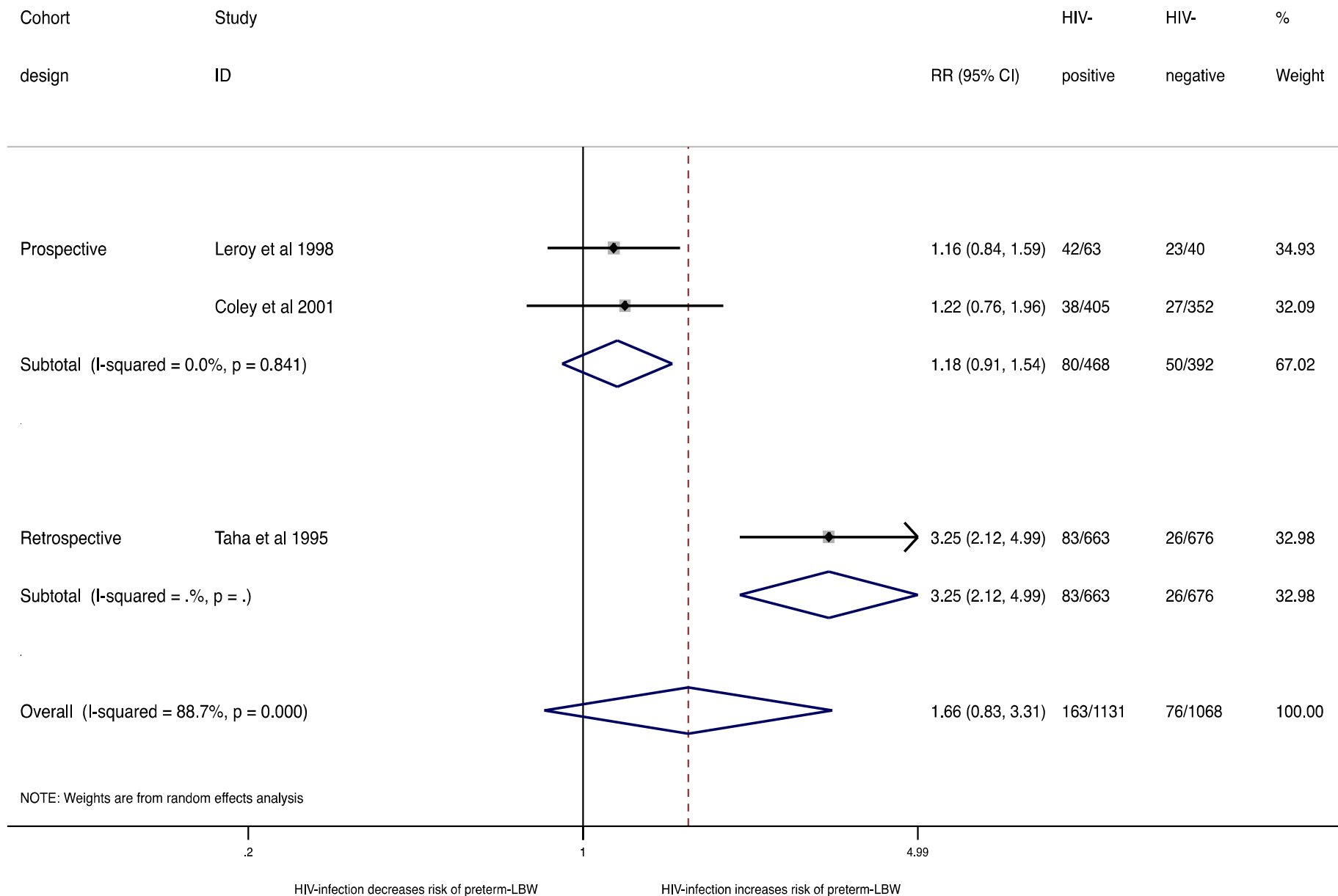
NOTE: Weights are from random effects analysis

HIV-infection decreases the risk of term-LBW HIV-infection increases the risk of term-LBW

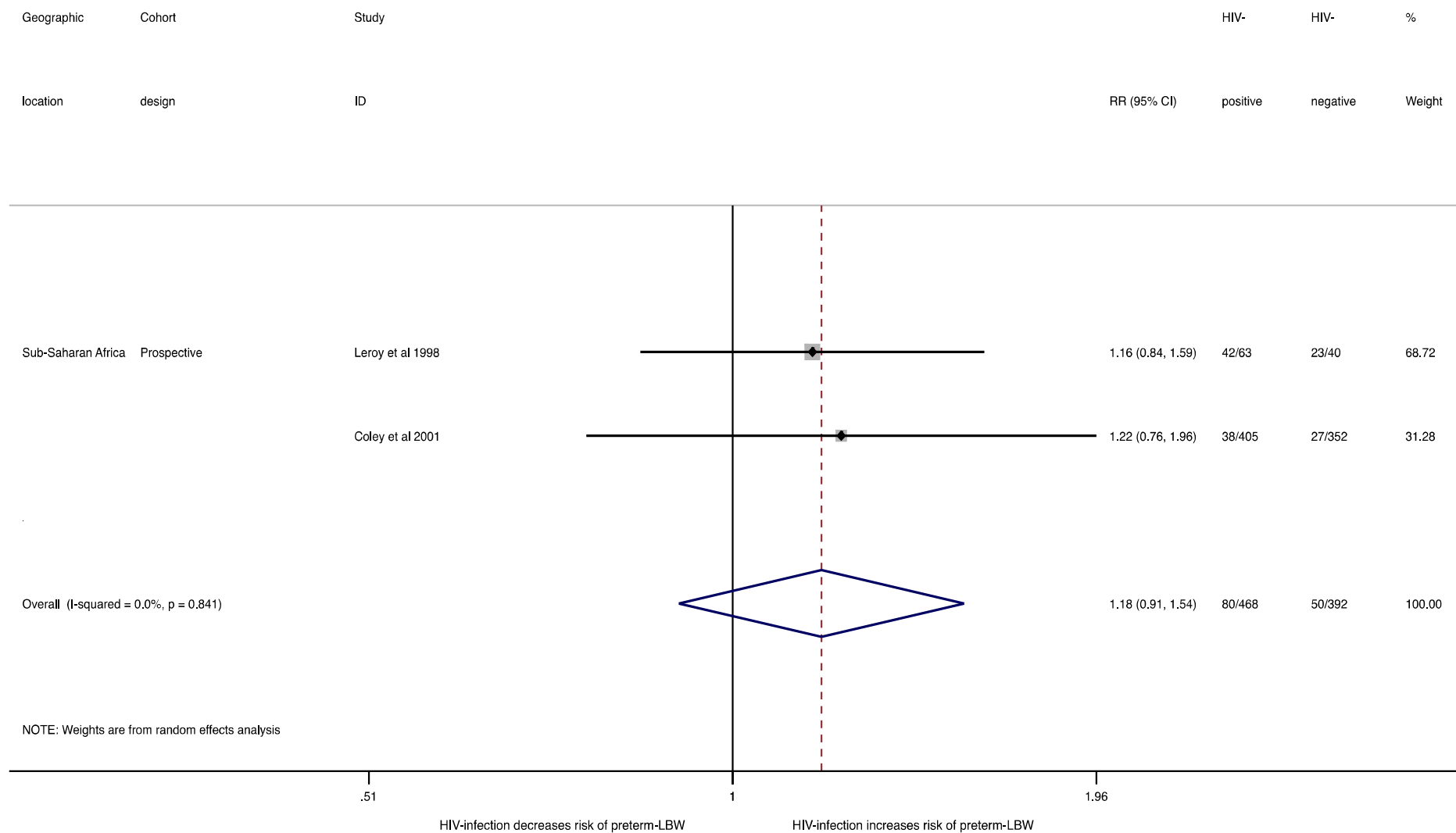
Appendix 13-28: Term-LBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective studies.



Appendix 13·29: Term-LBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective studies.



Appendix 13-30: Preterm-LBW associated with ART-naïve maternal HIV-infection, by study design.



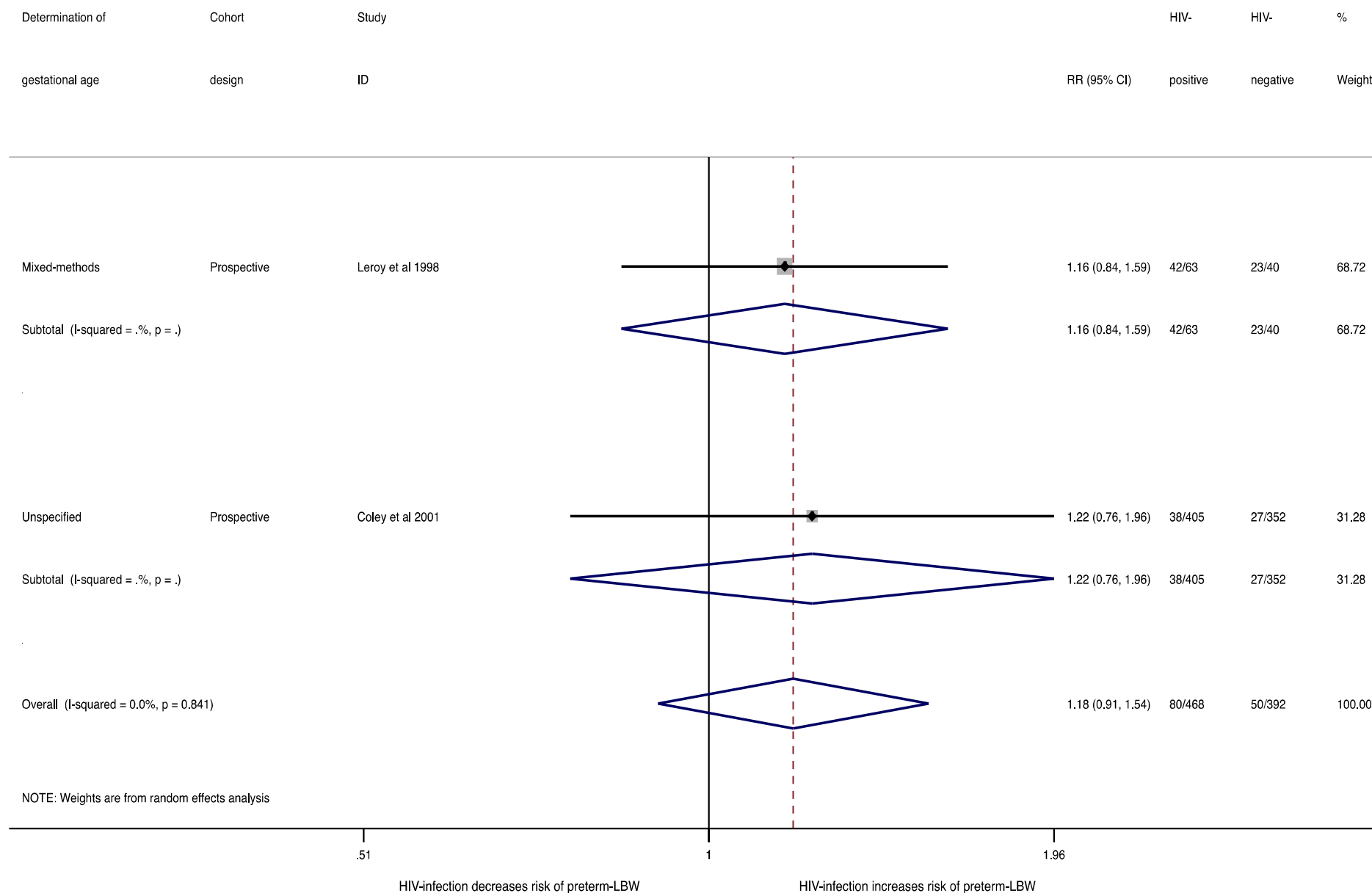
Appendix 13·31: Preterm-LBW associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.

Geographic	Cohort	Study	RR (95% CI)	HIV-	HIV-	%
location	design	ID		positive	negative	Weight
Sub-Saharan Africa	Retrospective	Taha et al 1995	3.25 (2.12, 4.99)	83/663	26/676	100.00
Overall (I-squared = .%, p = .)			3.25 (2.12, 4.99)	83/663	26/676	100.00

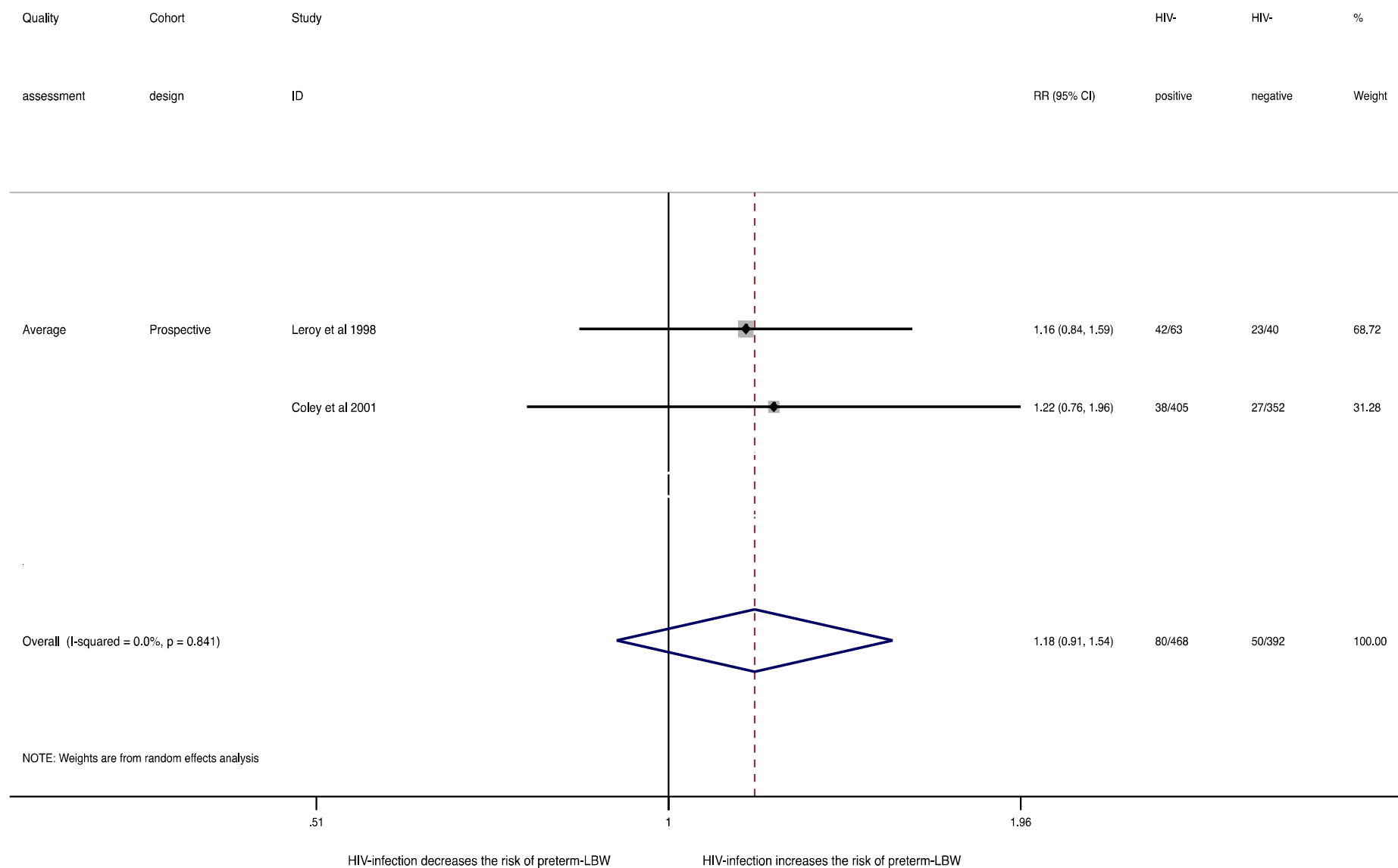
NOTE: Weights are from random effects analysis

HIV-infection decreases the risk of preterm-LBW HIV-infection increases the risk of preterm-LBW

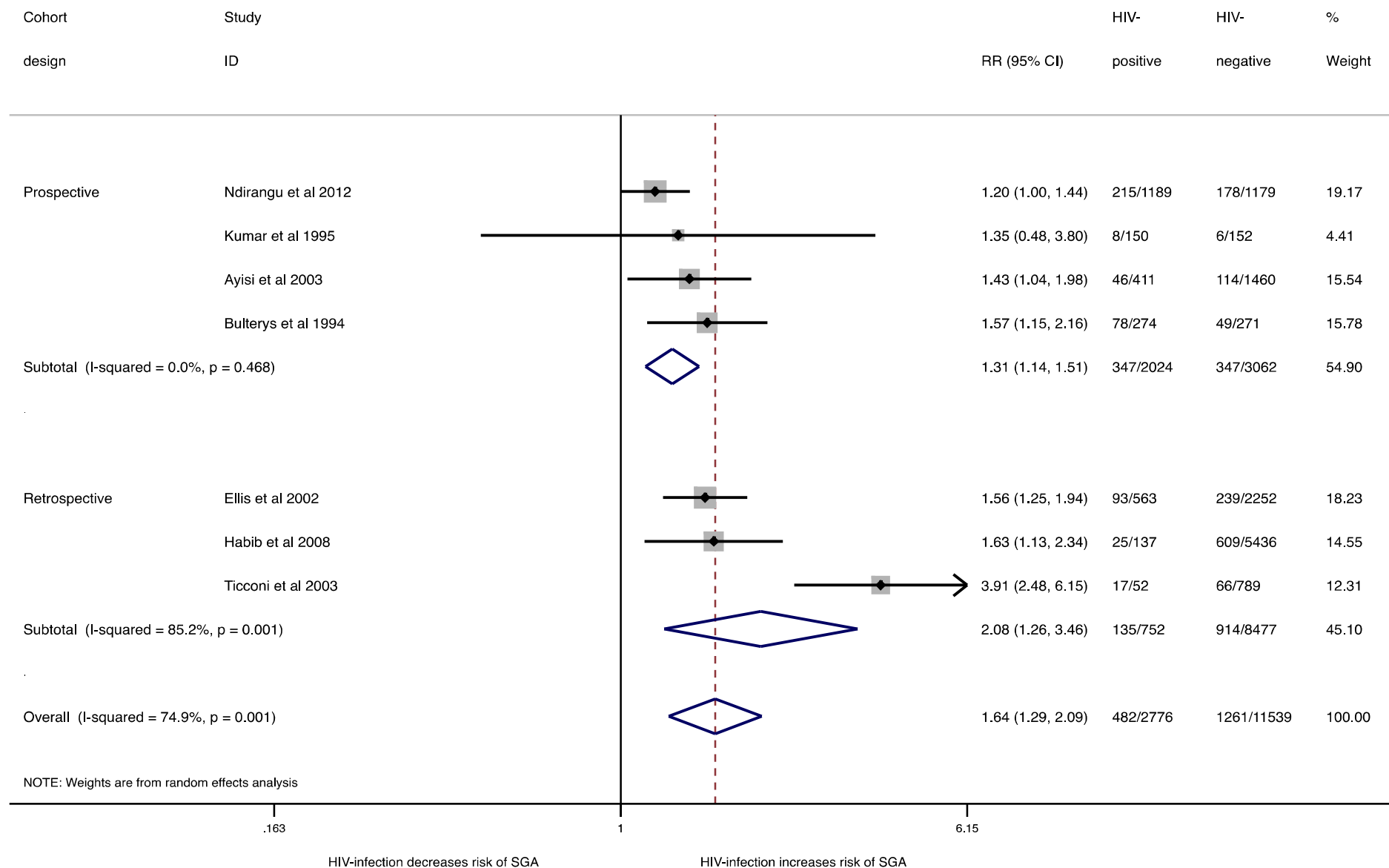
Appendix 13.32: Preterm-LBW associated with ART-naïve maternal HIV-infection, by geographic region: retrospective study.



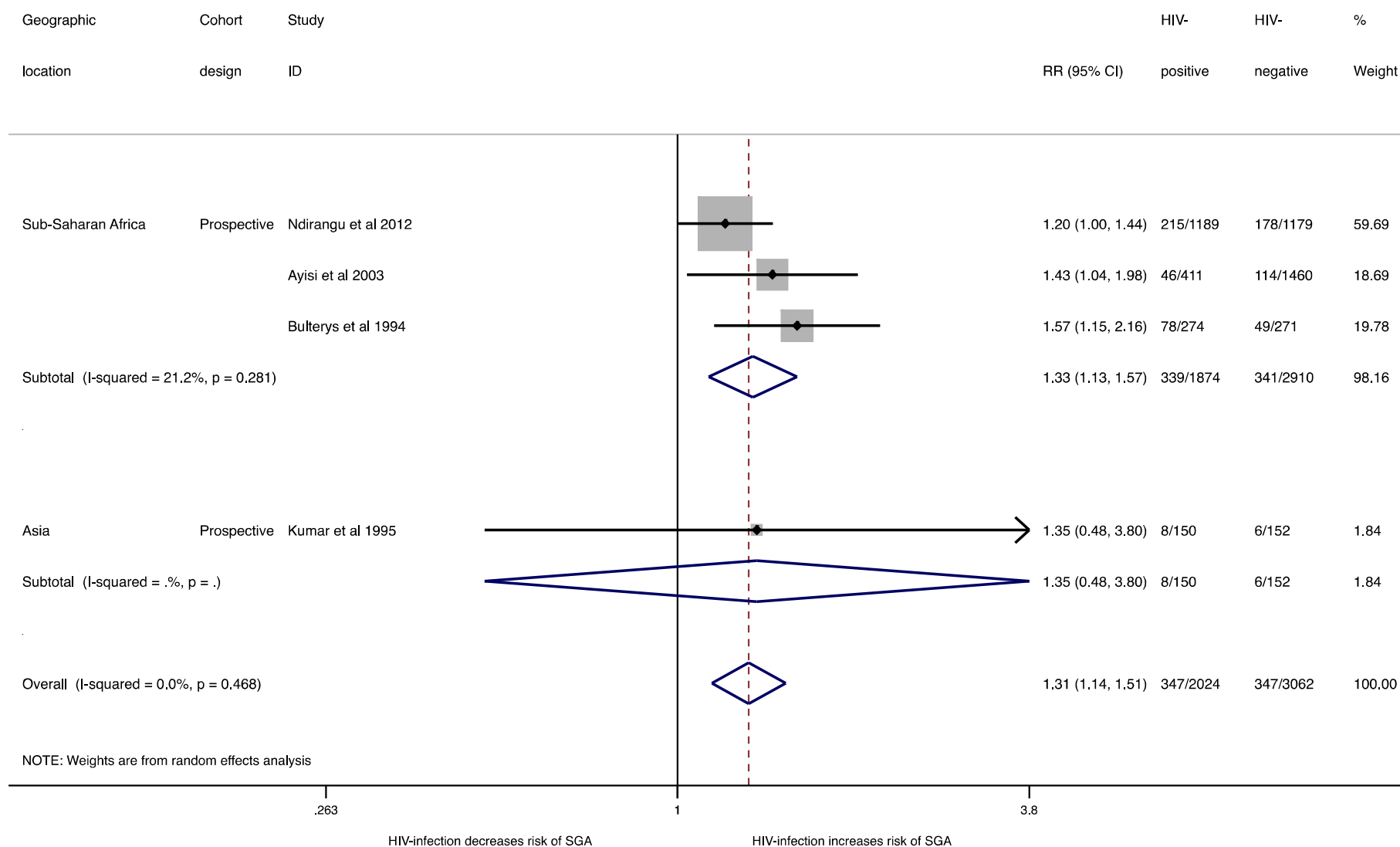
Appendix 13-33: Preterm-LBW associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: prospective studies.



Appendix 13·35: Preterm-LBW associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective studies.

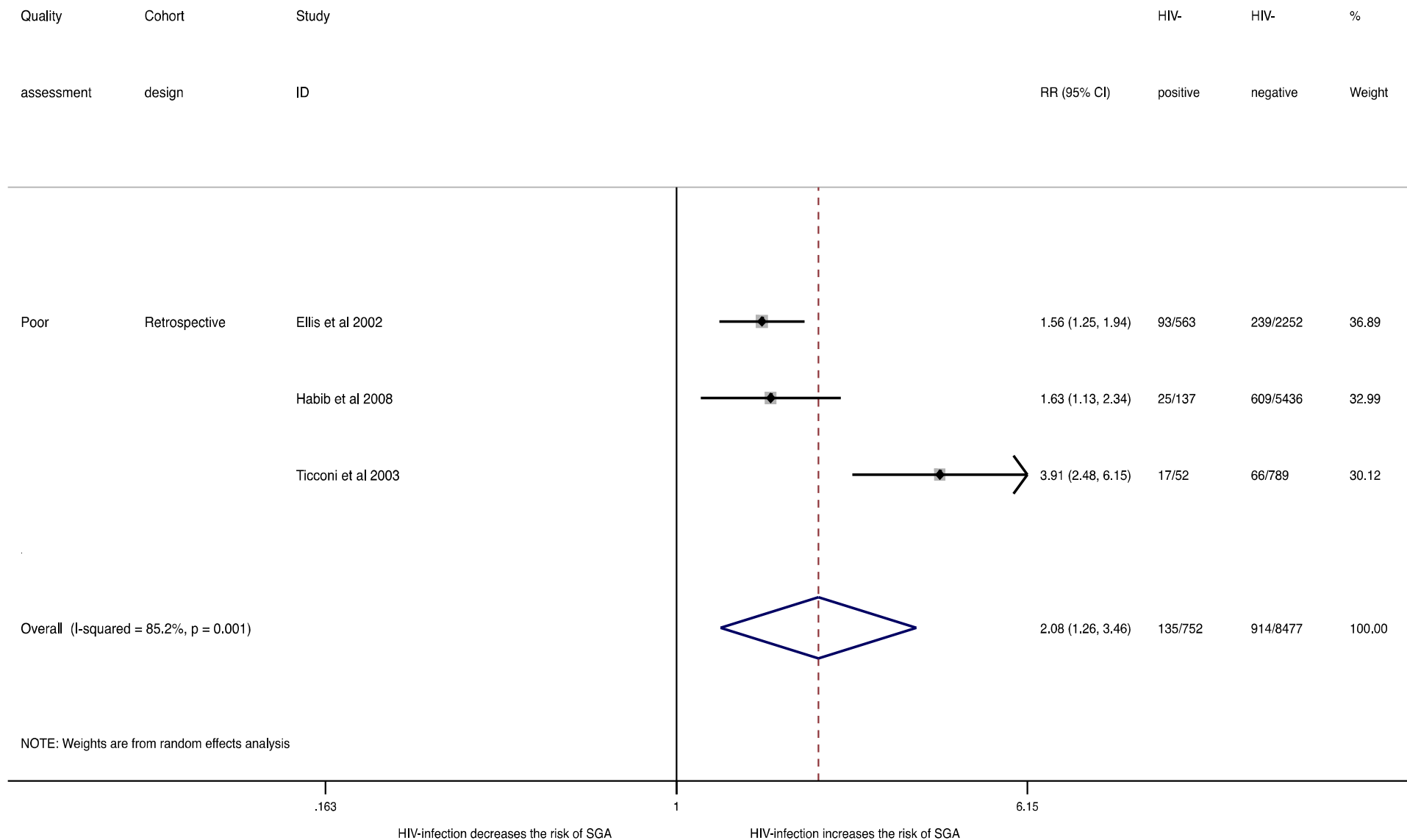


Appendix 13•37: SGA associated with ART-naïve maternal HIV-infection, by study design.

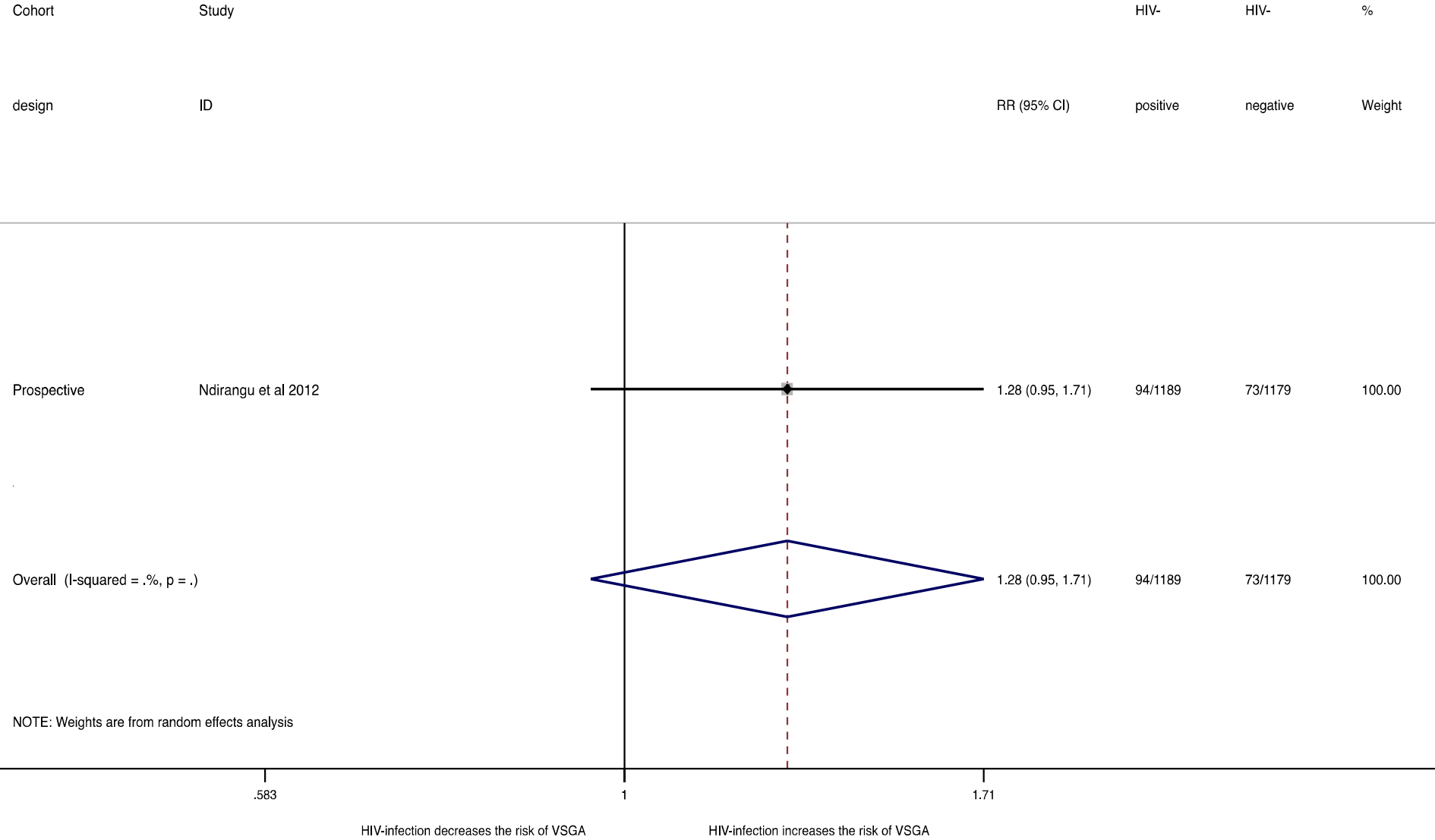


Appendix 13•38: SGA associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.

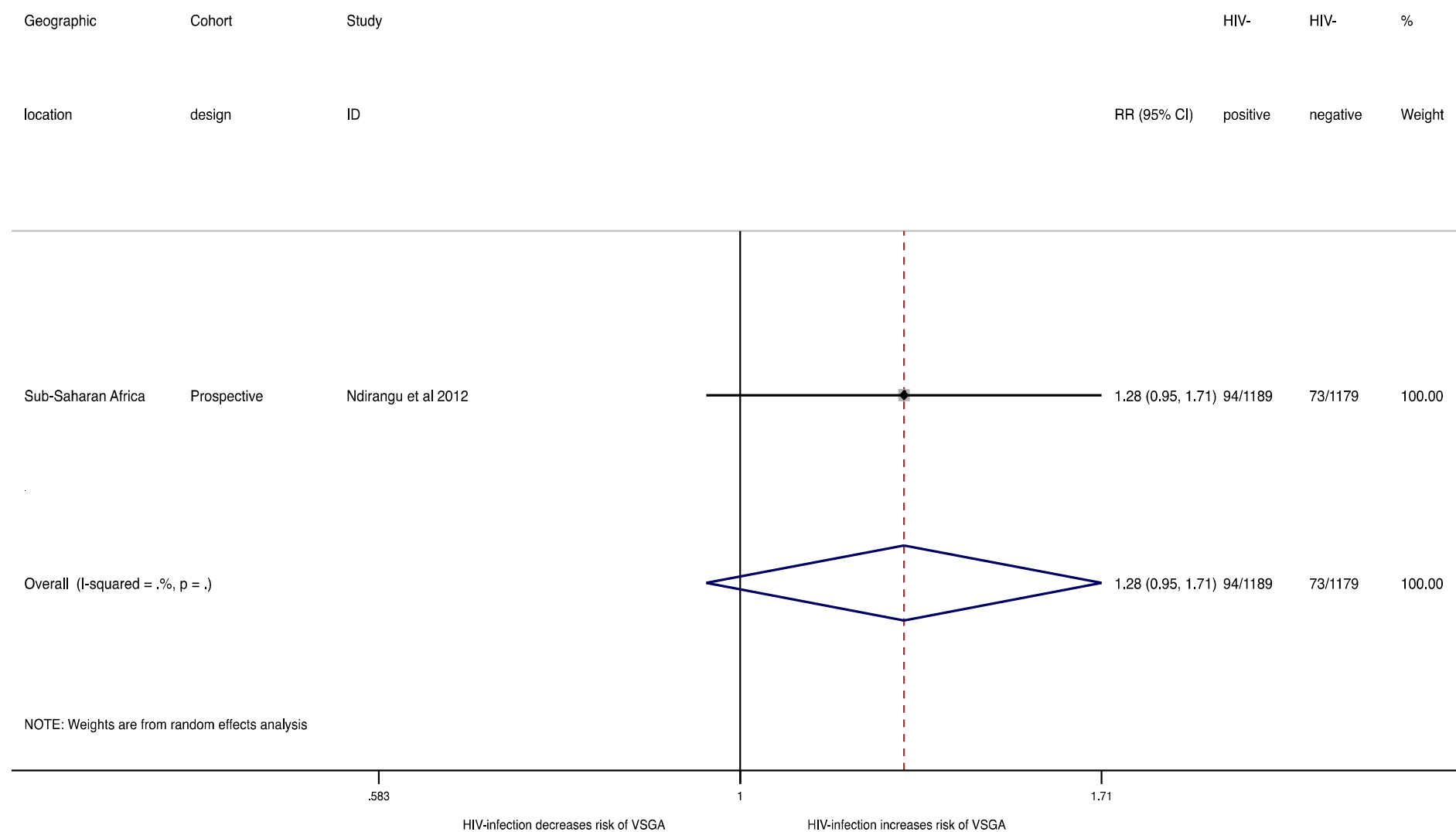
Determination of	Cohort	Study	RR (95% CI)	HIV- positive	HIV- negative	%
gestational age	design	ID				Weight
LNMP	Retrospective	Habib et al 2008	1.63 (1.13, 2.34)	25/137	609/5436	32.99
		Ticconi et al 2003	3.91 (2.48, 6.15)	17/52	66/789	30.12
		Subtotal (I-squared = 88.9%, p = 0.003)	2.50 (1.04, 5.97)	42/189	675/6225	63.11
Unspecified	Retrospective	Ellis et al 2002	1.56 (1.25, 1.94)	93/563	239/2252	36.89
Subtotal (I-squared = .%, p = .)			1.56 (1.25, 1.94)	93/563	239/2252	36.89
Overall (I-squared = 85.2%, p = 0.001)			2.08 (1.26, 3.46)	135/752	914/8477	100.00
NOTE: Weights are from random effects analysis						



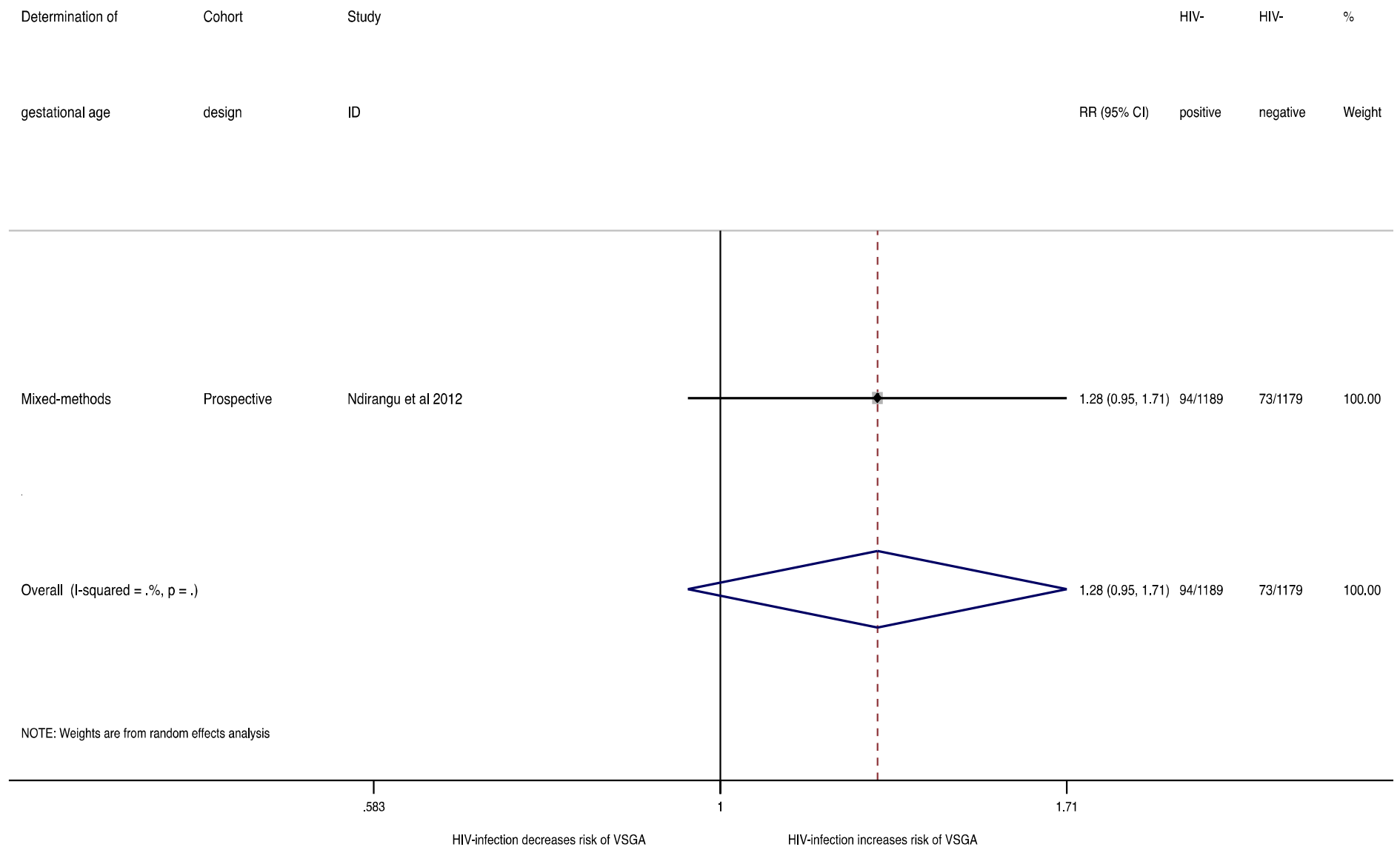
Appendix 13·43: SGA associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective studies.



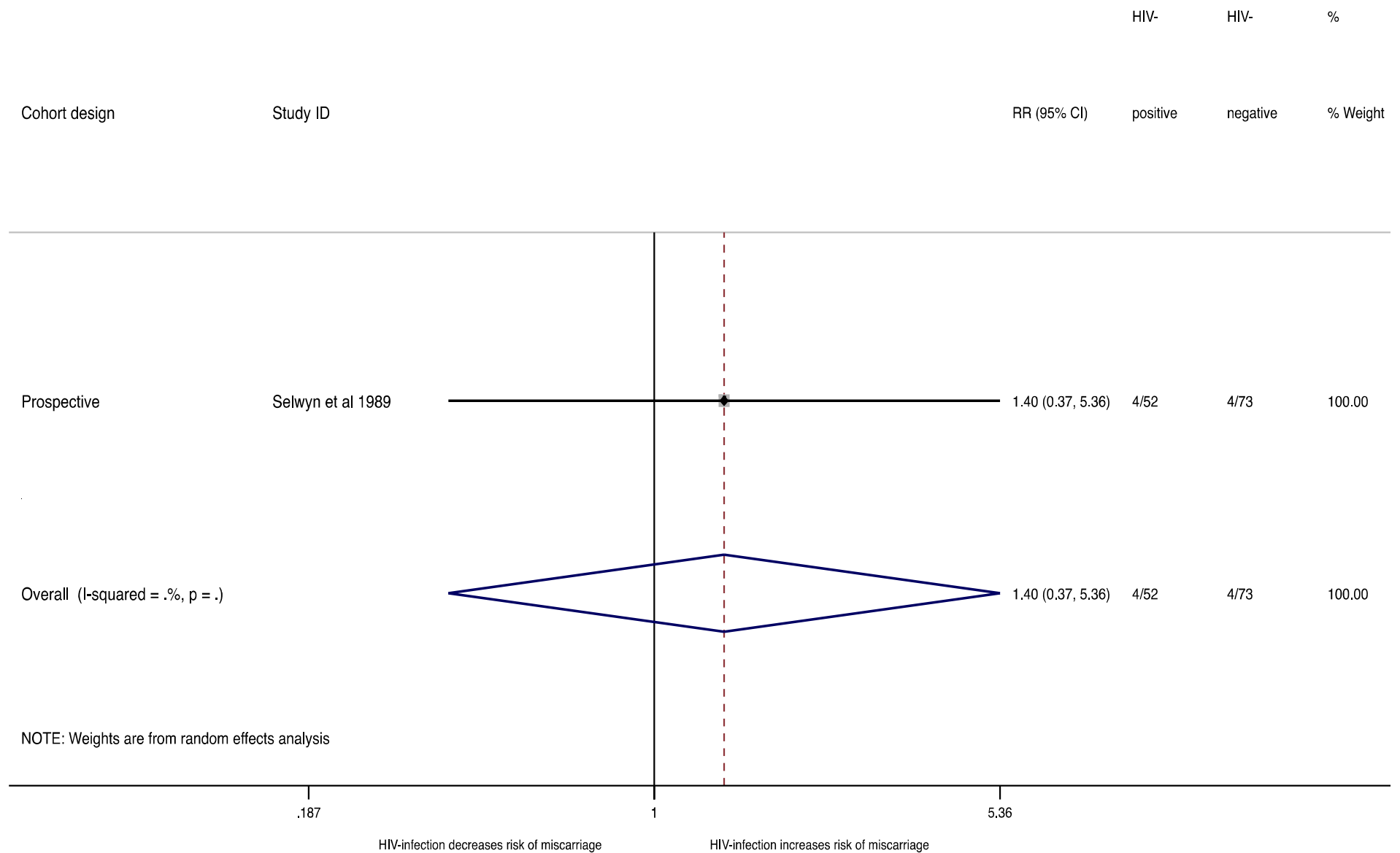
Appendix 13·44: VSGA associated with ART-naïve maternal HIV-infection, by study design.



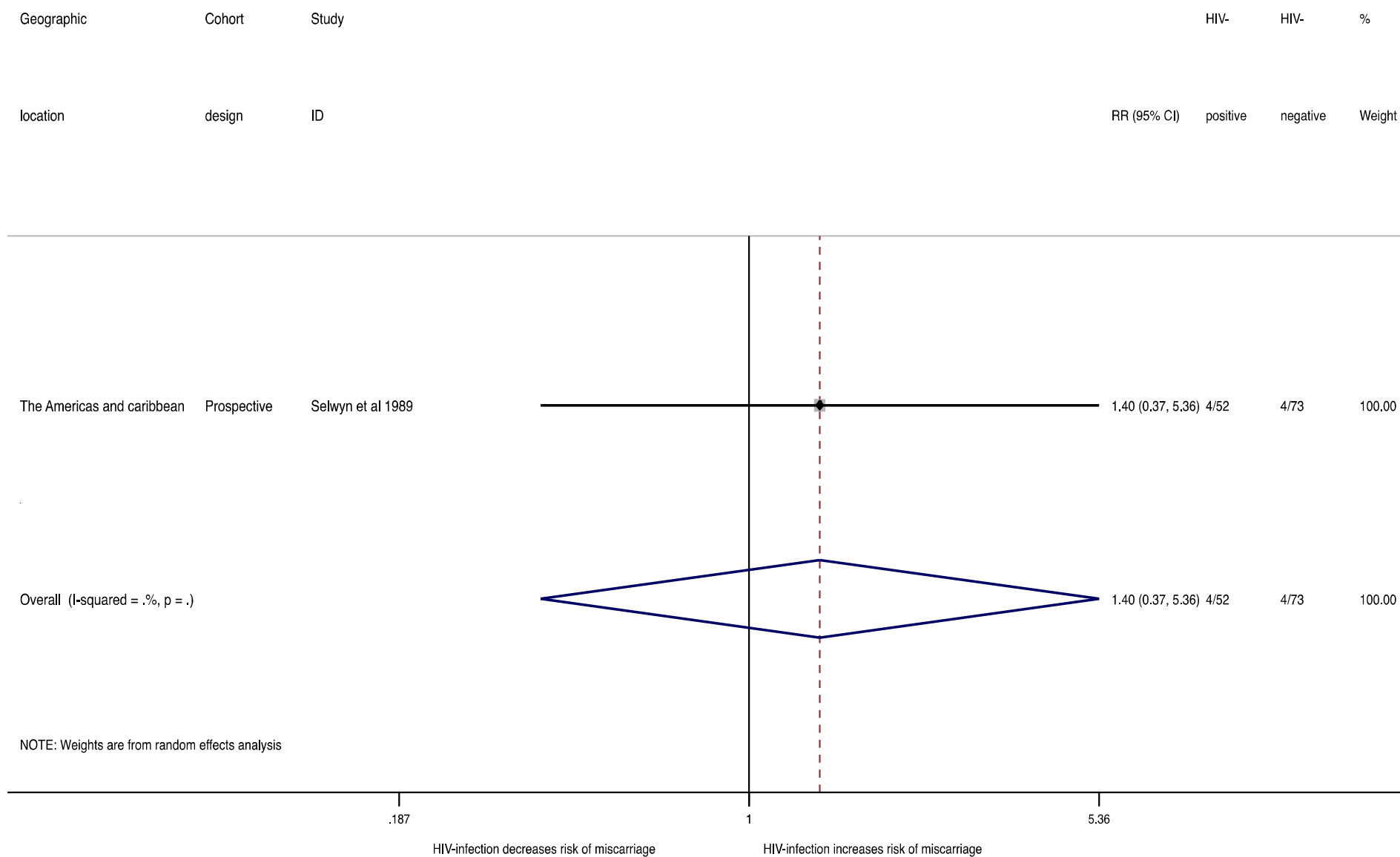
Appendix 13·45: VSGA associated with ART-naïve maternal HIV-infection, by geographic region: prospective study.



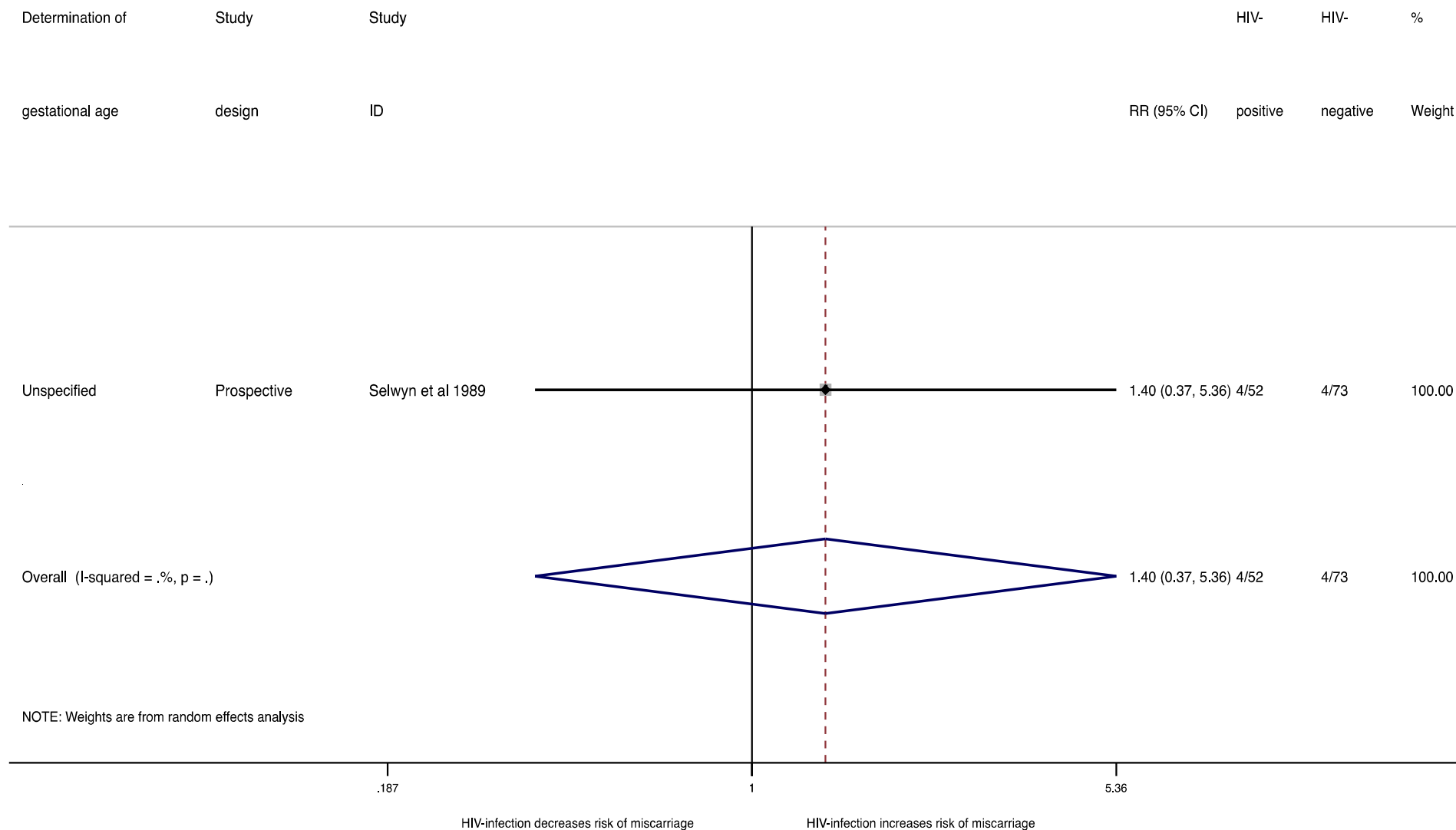
Appendix 13•46: VSGA associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: prospective study.



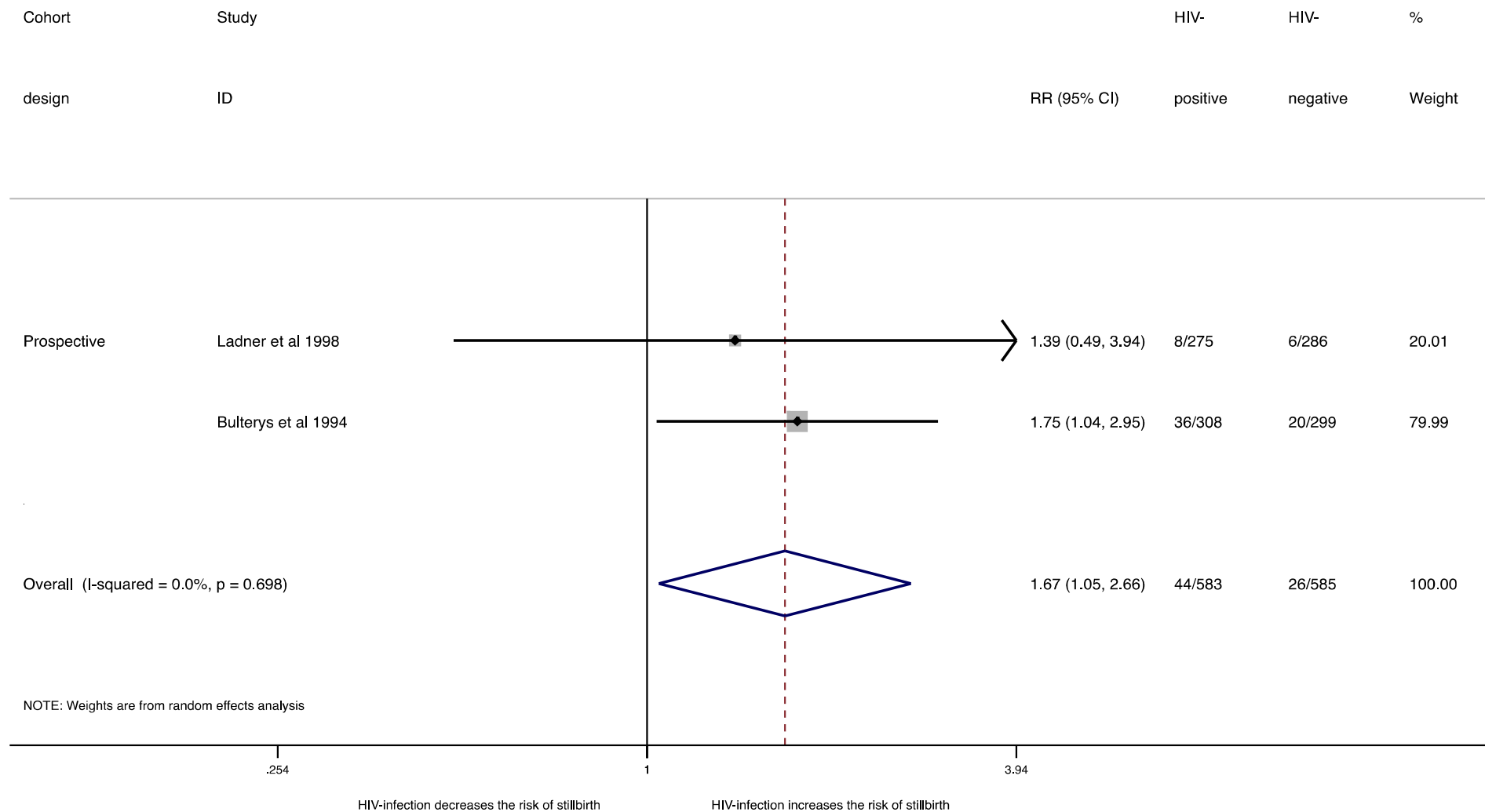
Appendix 13•48: Miscarriage associated with ART-naïve maternal HIV-infection, by study design.



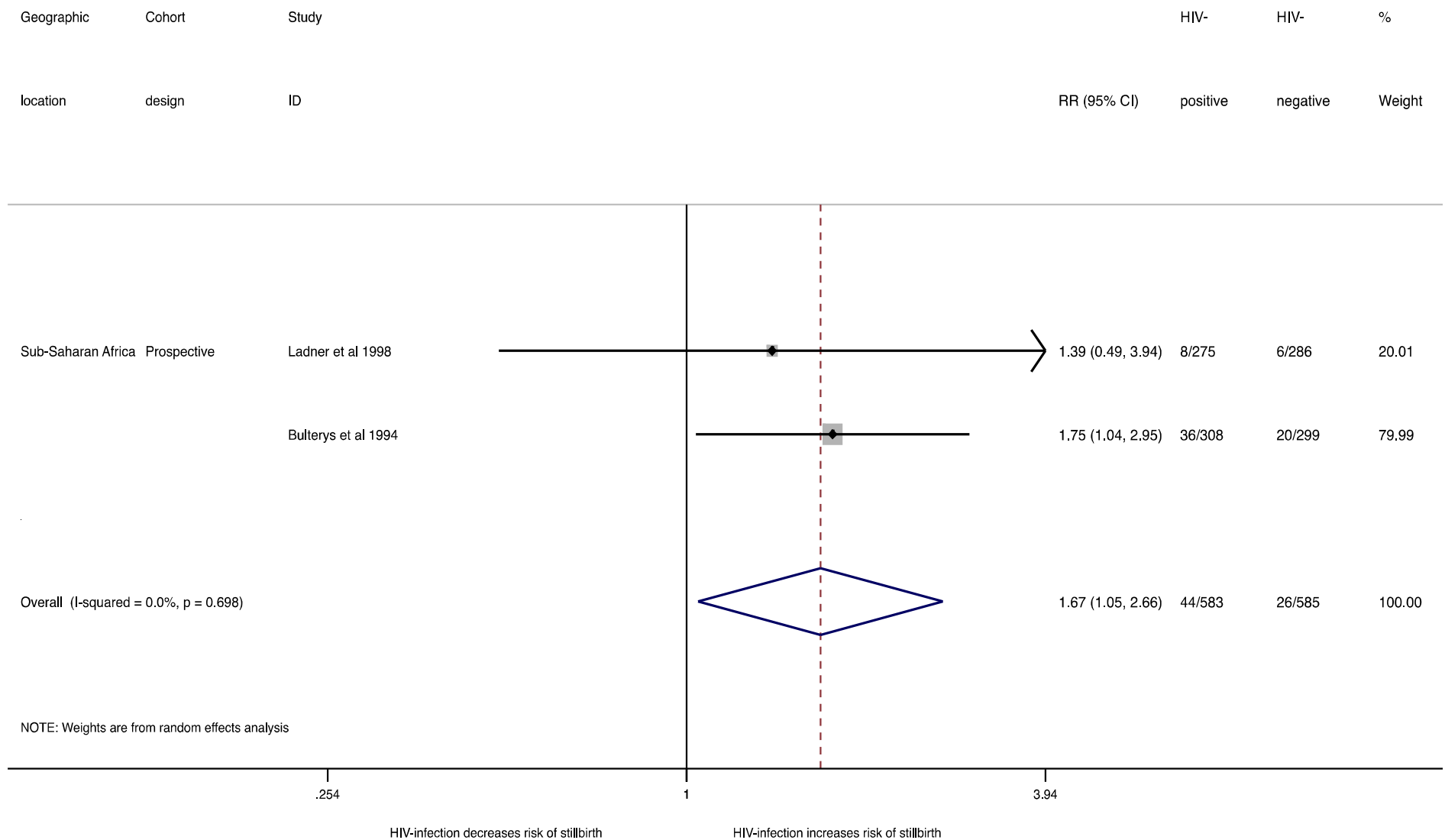
Appendix 13·49: Miscarriage associated with ART-naïve maternal HIV-infection, by geographic region: prospective study.



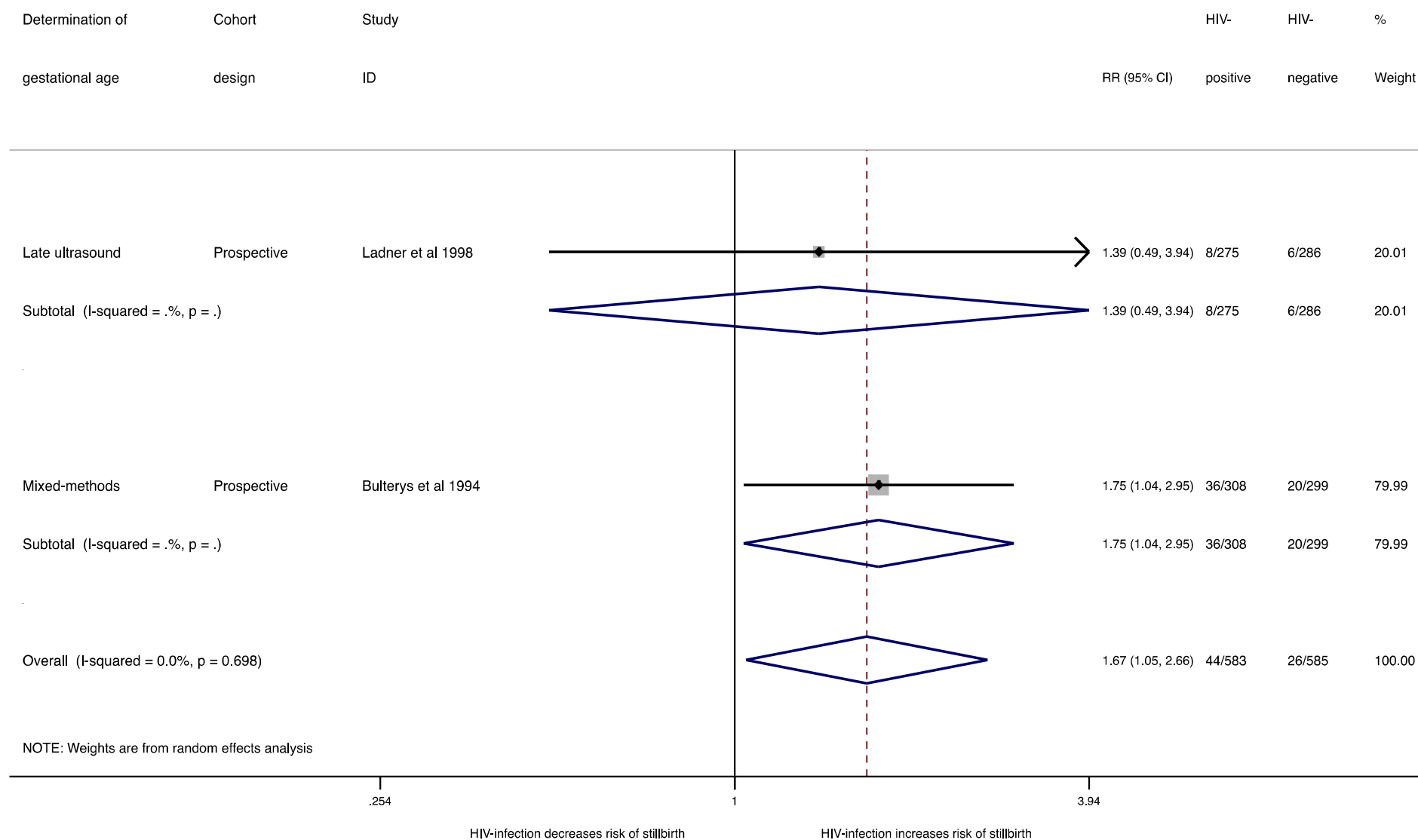
Appendix 13•50: Miscarriage associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: prospective study.



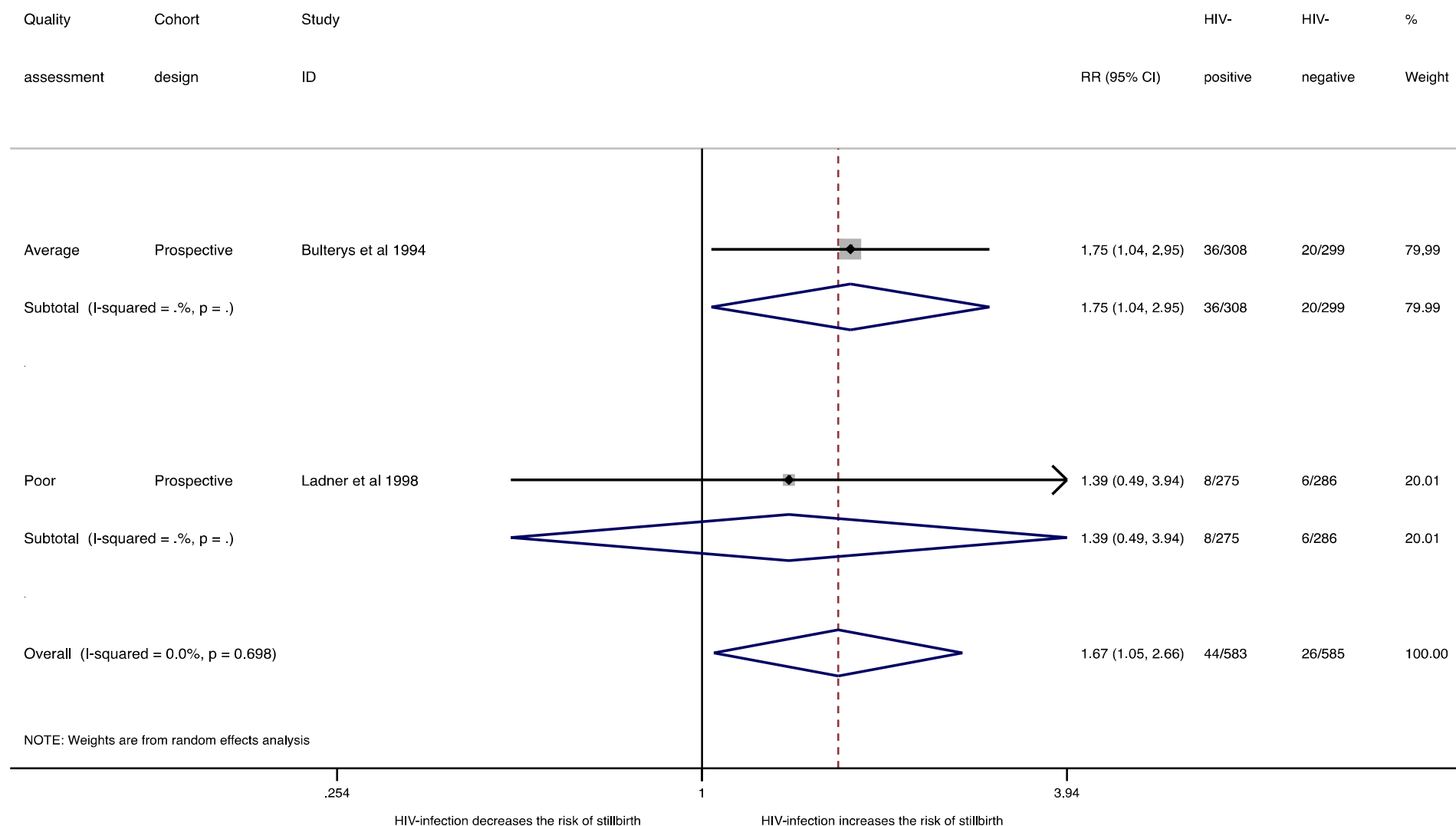
Appendix 13·52: Stillbirth associated with ART-naïve maternal HIV-infection, by study design.



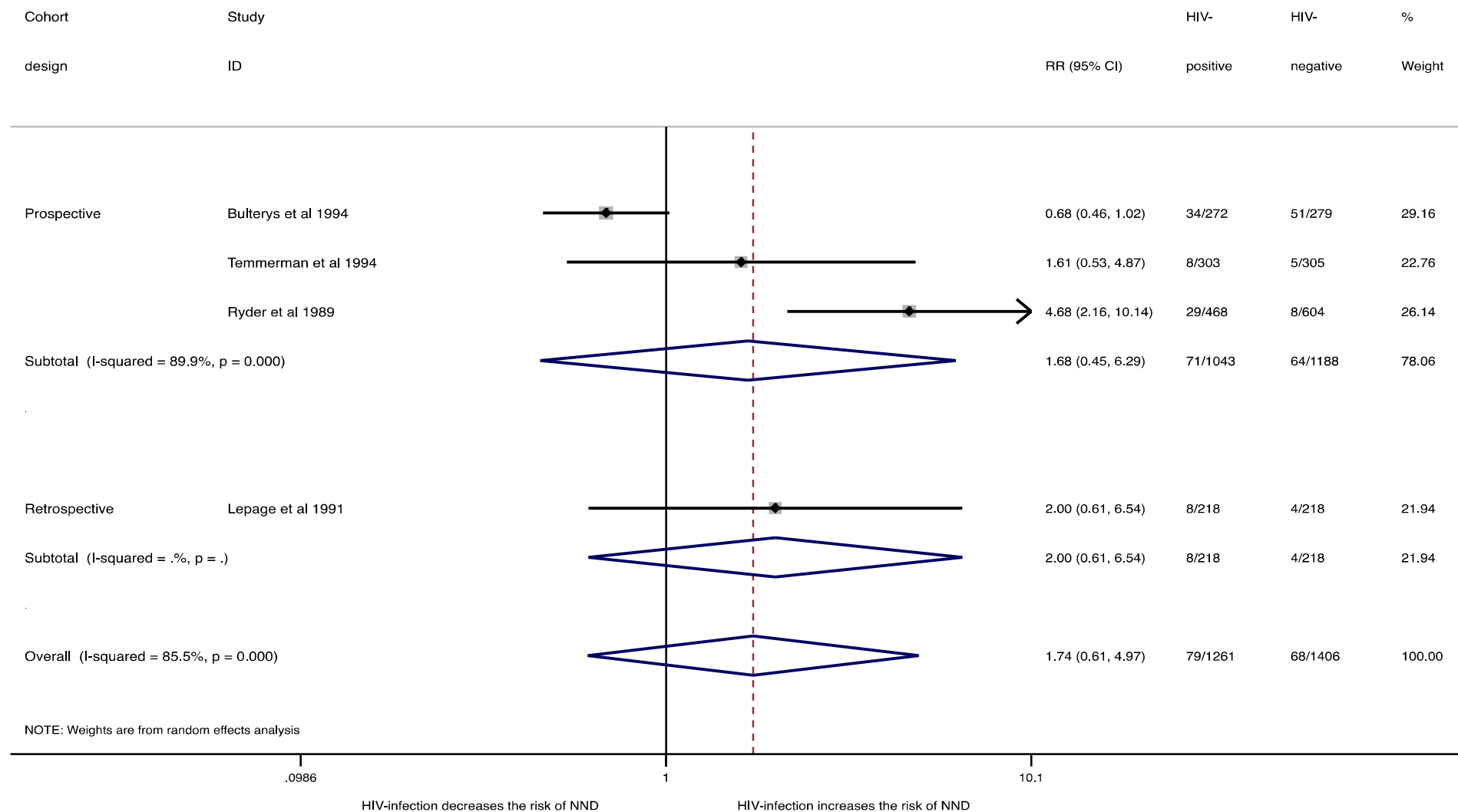
Appendix 13·53: Stillbirth associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.



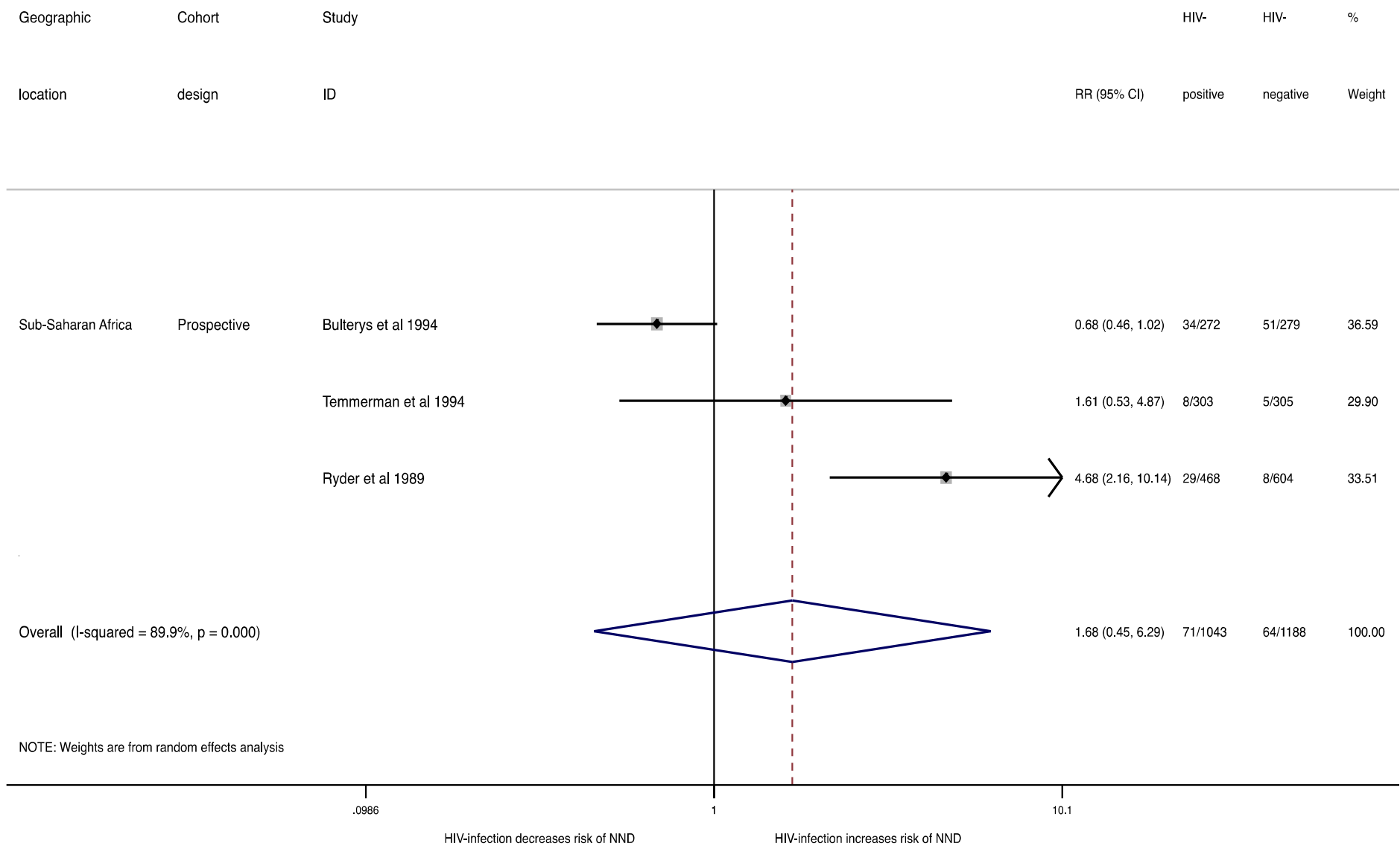
Appendix 13·54: Stillbirth associated with ART-naïve maternal HIV-infection, by method used to determine gestational age: prospective studies.



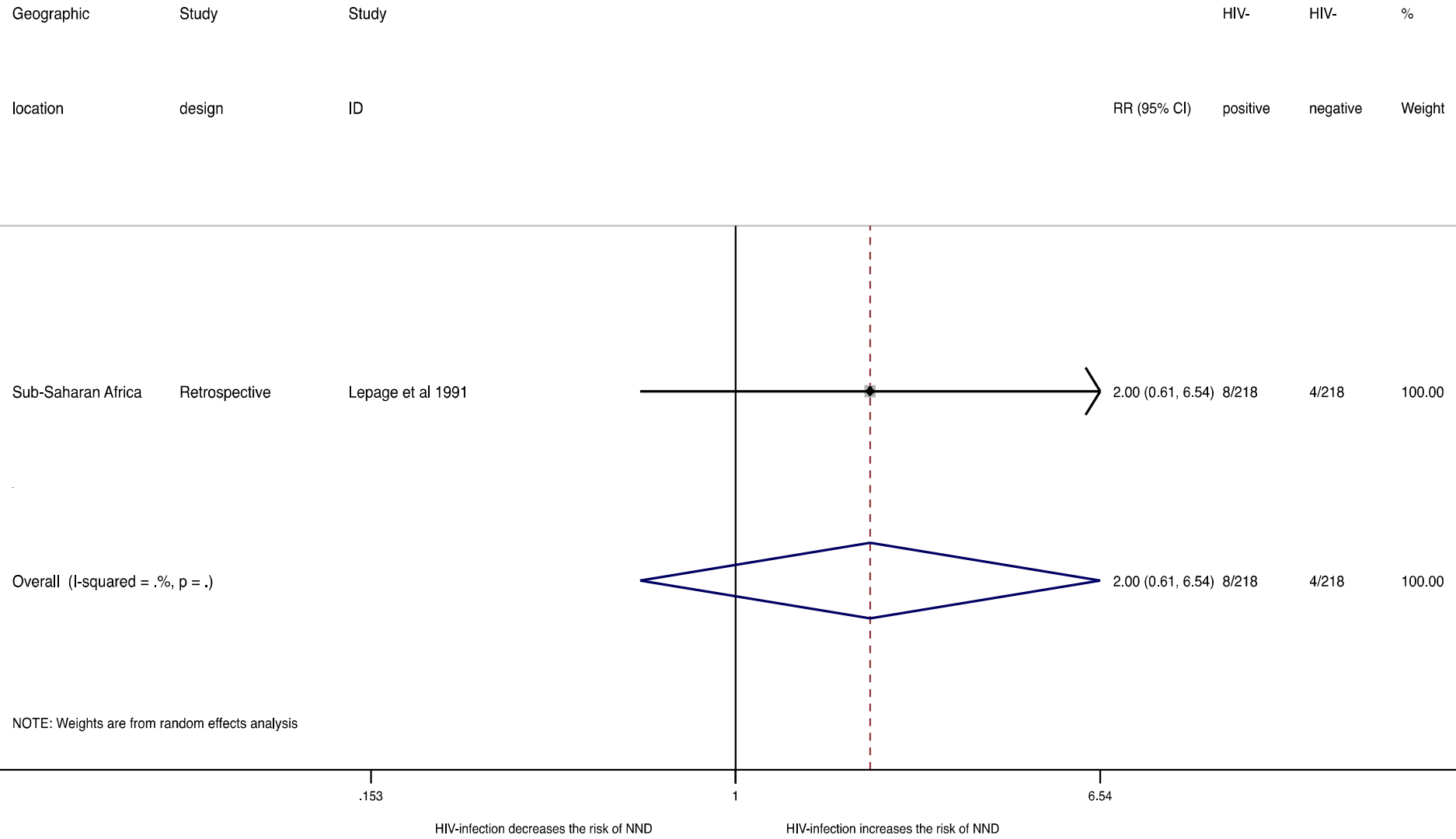
Appendix 13-55: Stillbirth associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective studies.



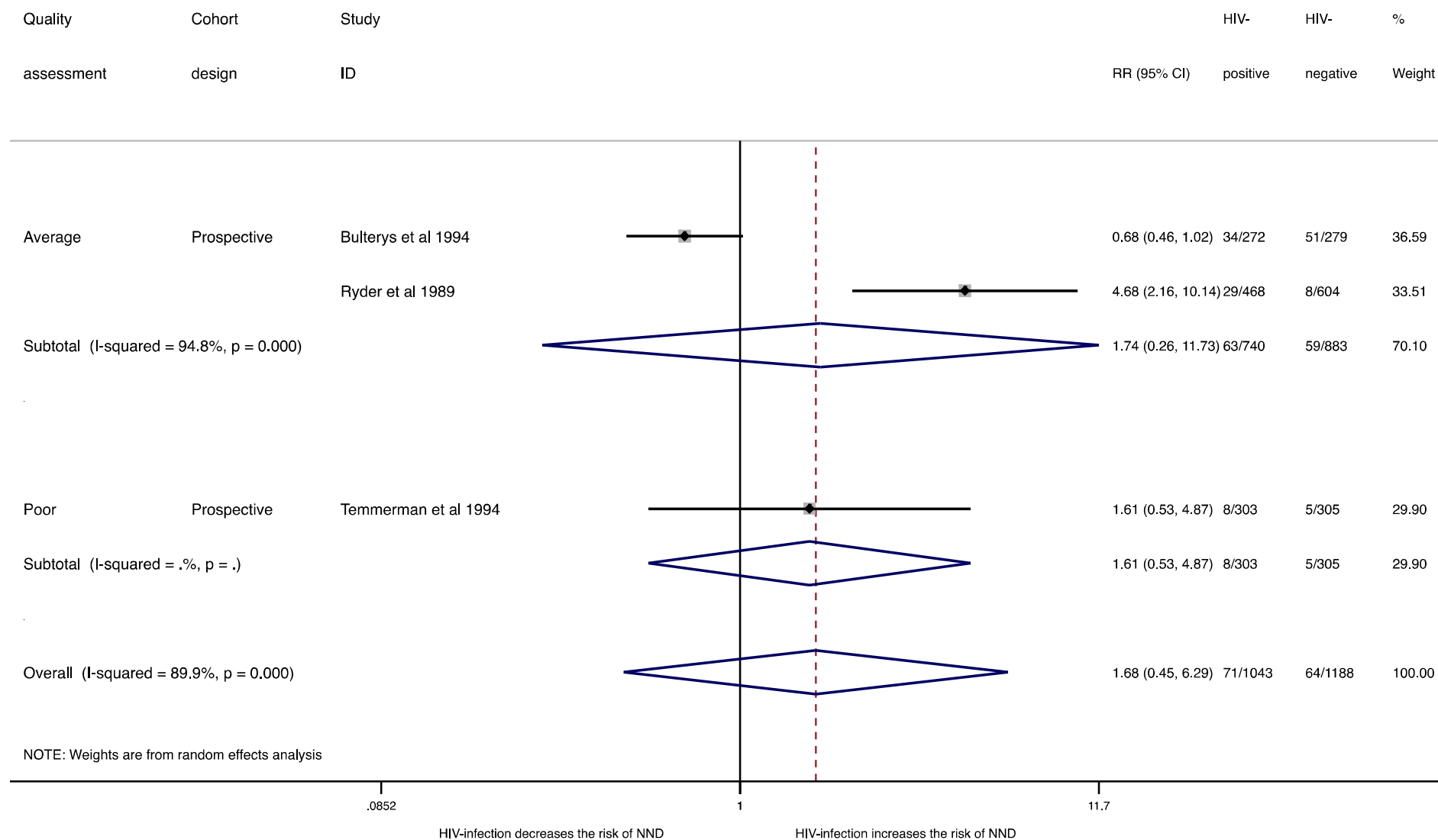
Appendix 13·56: NND associated with ART-naïve maternal HIV-infection, by study design.



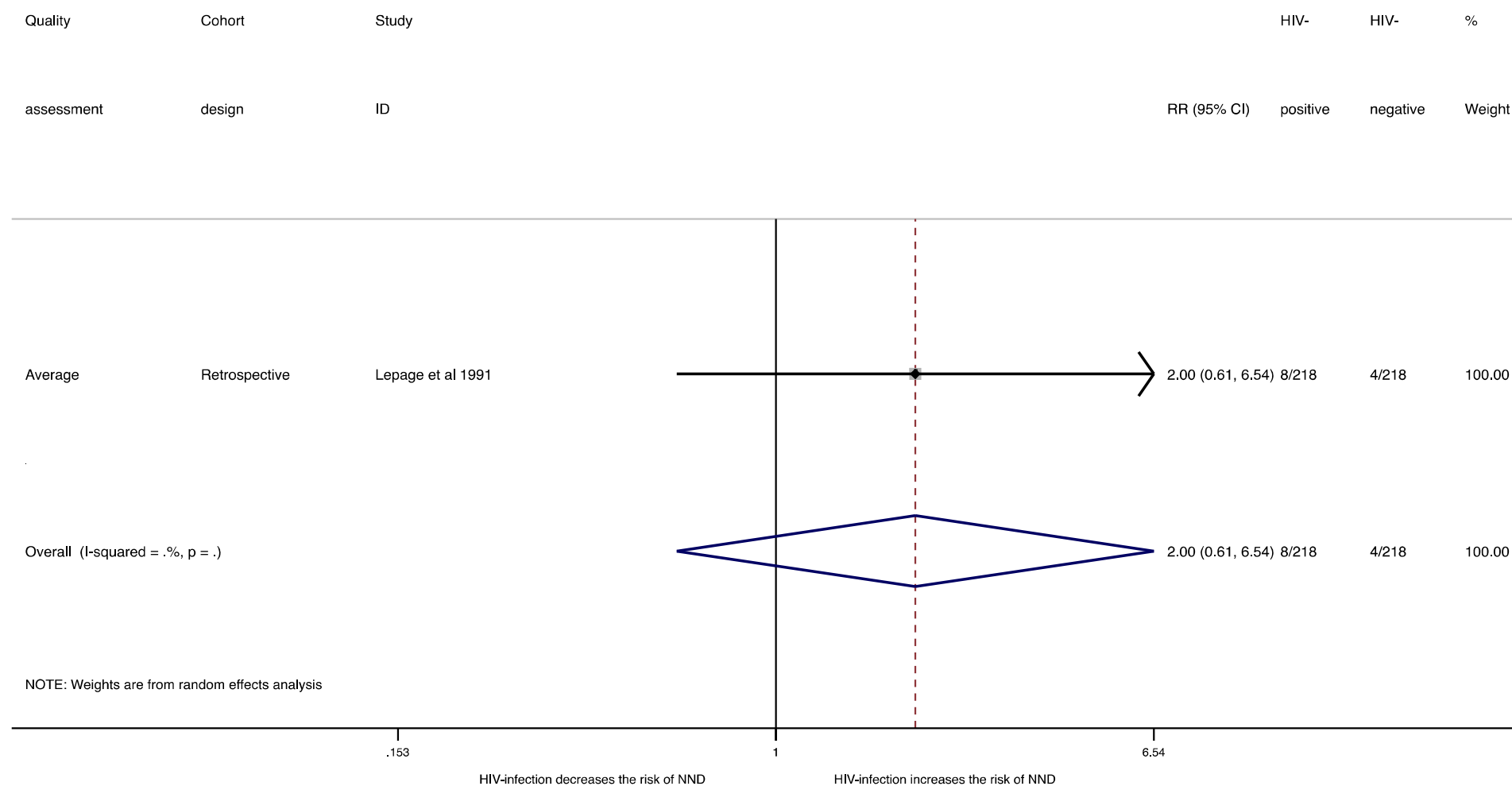
Appendix 13·57: NND associated with ART-naïve maternal HIV-infection, by geographic region: prospective studies.



Appendix 13·58: NND associated with ART-naïve maternal HIV-infection, by geographic region: retrospective study.



Appendix 13-59: NND associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: prospective studies.



Appendix 13•60: NND associated with ART-naïve maternal HIV-infection, by adapted Newcastle-Ottawa quality assessment of studies: retrospective study.