Perinatal outcomes in treated, HIV-positive pregnant women

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By

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Bismillahirrahmannirrahiim.

Innal hamda lillaah, nahmaduhu wa nasta'inuhu wa nastaghfiruh, wa na'udzu billaahi min syuruuri anfusinaa wa min sayyi'aati a'maalina. Man yahdihillaahu fa laa mudhilla lahu wa man yudhlilhu fa laa haadiya lah. Asyhadu an laa ilaaha illallaah wa anna Muhammadan abduhu wa rasuluh, ammaa ba'du.

Abstract

Globally, 1.4 million HIV-positive women become pregnant annually, of whom 92% reside in sub-Saharan Africa and 23% in South Africa. In 2019, 87% of HIV-positive pregnant women in sub-Saharan Africa and >97% in South Africa received lifelong antiretroviral therapy (ART) for the prevention of mother-to-child transmission (MTCT). However, the evidence regarding the association between maternal HIV/ART and perinatal outcomes has been inconsistent. This is partly due to the reliance on observational data and the use of sub-optimal methods to estimate gestational age and measure birth weight. Furthermore, the effect of maternal HIV/ART on fetal growth patterns has never been evaluated.

This thesis, therefore, aimed to explore the effect of maternal HIV/ART on perinatal outcomes and fetal growth patterns. First, a systematic review and pairwise meta-analysis of observational studies was performed. Data from a prospective longitudinal study in South Africa were then analysed to assess those effects in a "real world" context. Gestational age was accurately estimated using first trimester ultrasound (<14 weeks' gestation). Fetal biometric parameters (biparietal diameter [BPD], head circumference [HC], abdominal circumference [AC] and femur length [FL]) were measured serially from 14 weeks' gestation to delivery. Birth weight was measured in a standardised manner within 24h of birth.

The systematic review and meta-analysis showed that treated maternal HIV infection was associated with an increased risk of preterm birth (PTB), spontaneous PTB (sPTB), very PTB (VPTB), low birth weight (LBW) and small for gestational age (SGA) compared with HIV-negativity. However, treated maternal HIV infection was associated with a reduced risk of PTB, LBW and very LBW (VLBW) compared with untreated maternal HIV infection. Among treated HIV-positive women: 1) highly active antiretroviral therapy (HAART) was associated with PTB, LBW and SGA; 2) protease inhibitor (PI)-based ART was associated with PTB, and 3) pre-conception initiation of ART was associated with PTB and VPTB. Secondly, based on accurately determined gestational age and birth weight in the longitudinal study, the overlap between PTB and LBW was substantial, i.e. it is not worthwhile to analyse them separately. Thirdly, the multiple logistic regression showed a significant association between maternal HIV/ART and SGA and neonatal death. Risk factors for adverse perinatal outcomes were also identified: in HIV-positive women, these were dominated by nutritional factors. Lastly, the growth trajectories of fetal BPD, HC, AC and FL were similar between treated HIV-positive and HIV-negative women.

Given the clear benefits of ART for improving maternal health and reducing MTCT risk, the expansion of ART coverage in women of reproductive age should be accelerated. However, the present findings of an unintended negative effect of maternal HIV/ART on perinatal outcomes highlight the importance of ongoing surveillance to assess the safety of *in utero* ART exposure. Accurate measurement of perinatal outcomes is essential to provide better evidence. Therefore, expansion of ultrasound access and standardised birth weight measurement within 24h of birth should be promoted, particularly in HIV-endemic settings with poor perinatal outcomes and the highest fertility rates, i.e. sub-Saharan Africa.

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I would like to express my deep and sincere gratitude to my supervisors, Professor Stephen Kennedy, Dr. Eleonora Staines-Urias and Dr. Joris Hemelaar, for all the guidance and supervision, motivation and immense knowledge over these years. Their guidance helped me throughout my studies and writing of this thesis. I wish to thank Dr. Eric Ohuma for advising me on the statistical analysis of fetal growth patterns. I am extending my thanks to Professor Krina Zondervan and Dr. Karl Morten for all their support and guidance. I gratefully acknowledge all the study participants whose data contributed to this study; Dr. Chrystelle Tshivuila-Matala who collected much of the primary data, and the doctors, nurses and staff at Chris Hani Baragwanath Academic Hospital (Department of Obstetrics and Gynaecology) who facilitated the study. I greatly appreciate the sonographers who performed the ultrasound scans and the anthropometrists who weighed the newborns. I wish to acknowledge the Indonesia Endowment Fund for Education (Lembaga Pengelola Dana Pendidikan) for a full doctorate scholarship.

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Contribution to this thesis

Chapter 3: Systematic review

The present systematic review is under the umbrella of a systematic review project focusing on adverse perinatal outcomes in HIV-positive pregnant women on ART, supervised by Professor Stephen Kennedy and Dr. Joris Hemelaar. I took the lead on every stage of the conduct of the systematic review of observational studies. I wrote a systematic review protocol, updated the list of search terms and conducted the search of conference abstracts. Systematic literature searches of the general databases were conducted by a specialist librarian (SK). First reviewers (CS, MK and ZB) screened the titles and abstracts of all retrieved articles, identified all full text articles and abstracts, assessed whether each study met the eligibility criteria, conducted the assessment of methodological quality, extracted all the data, and conducted hand searches of references of all included studies and previous systematic reviews. All of these were then checked by me as a second reviewer. I conducted all the pairwise meta-analyses under the guidance of Professor Stephen Kennedy, Dr. Joris Hemelaar and Dr. Eleonora Staines-Urias. All statistical analyses were performed under the guidance of Dr. Eleonora Staines-Urias. I wrote the thesis chapter under the supervision of Professor Stephen Kennedy and Dr. Eleonora Staines-Urias.

Chapter 4: Overlap analysis, Chapters 5 and 6: Cohort analysis

These chapters analysed data collected previously by the INTERBIO-21st Study conducted in Soweto, South Africa. Under the guidance of Professor Stephen Kennedy and Dr. Joris Hemelaar, I wrote the study protocol to analyse the data, applied for and received ethical approval from the Human Research Ethics

Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa. I requested the dataset from the INTERBIO-21st Study Team and antenatal CD4 data from the National Health Laboratory Service (NHLS), South Africa. I cleaned the final dataset analysed in these chapters. I conducted all statistical analyses, generated all figures and tables under the guidance of Dr. Eleonora Staines-Urias. I wrote the thesis chapters under the supervision of Professor Stephen Kennedy and Dr. Eleonora Staines-Urias. The preliminary results of Chapter 5 were presented at the International AIDS Conference (Amsterdam, 2018, poster presentation). I am the first author on one manuscript based on the findings presented in Chapter 5 under the guidance of Professor Stephen Kennedy, Dr. Joris Hemelaar and Dr. Eleonora Staines-Urias. The list of publication and conference abstracts arising from the present work is presented in Appendix 1.

Chapter 7: Fetal growth patterns

I wrote the study protocol under the guidance of Professor Stephen Kennedy and Dr. Eleonora Staines-Urias. I requested the longitudinal data of fetal biometric parameters from the INTERBIO-21st Study Team. I cleaned the final dataset analysed in this chapter. I conducted all statistical analyses, generated all figures and tables under the guidance of Dr. Eleonora Staines-Urias and Dr. Eric Ohuma. I wrote the thesis chapter under the supervision of Professor Stephen Kennedy and Dr. Eleonora Staines-Urias.

I dedicate this thesis to
Allah Subhanahu Wa Ta'ala and
His Messenger Prophet Muhammad Shallallaahu 'Alaihi Wa Sallam.
My parents for their constant support and unconditional love,
I love you both dearly.

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List of abbreviations

3TC	Lamivudine
AARR	Average annual reduction rate
ABC	Abacavir
AC	Abdominal circumference
ACOG	American College of Obstetricians and Gynecologists
ACTG	AIDS Clinical Trials Group
AEDF	Absent end-diastolic flow
AGA	Appropriate for gestational age
AI	Attachment inhibitor
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AMANHI	Alliance for Maternal and Newborn Health Improvement
ANC	Antenatal care
APV	Amprenavir
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
AZT	Zidovudine
BIC	Bictegravir
BMI	Body mass index
BPD	Biparietal diameter
BW	Birth weight
CA	CCR5 antagonist
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDC	Centers for Disease Control and Prevention
CHBAH	Chris Hani Baragwanath Academic Hospital
CI	Confidence interval
cm	Centimetre

COBI	Cobicistat
CPR	Cerebroplacental ratio
CRL	Crown-rump length
CROI	Conference on Retroviruses and Opportunistic Infections
CXCR4	C-X-C chemokine receptor type 4
d4T	Stavudine
DALYs	Disability-adjusted life-years
DC	Dendritic cell
ddI	Didanosine
dL	Decilitre
DLV	Delavirdine
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DOR	Doravirine
DR Congo	Democratic Republic of Congo
DRV	Darunavir
DTG	Dolutegravir
ECS	European Collaborative Study
EFV	Efavirenz
EFW	Estimated fetal weight
Env	Envelope protein
ETR	Etravirine
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FI	Fusion inhibitor
FL	Femur length
FP2	Second-order fractional polynomials
FPV	Fosamprenavir
FTC	Emtricitabine
FTR	Fostemsavir
GA	Gestational age

Gag	Group-specific antigen
GBD	Global Burden of Disease
GH	Growth hormone
Gp120	120kDA envelope glycoprotein surface subunit
Gp41	41kDA envelope glycoprotein transmembrane subunit
GWG	Gestational weight gain
HAART	Highly active antiretroviral therapy
Hb	Haemoglobin
HC	Head circumference
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HELLP	Haemolysis, elevated liver enzymes, low platelet
HIV	Human immunodeficiency virus
HIVR4P	HIV Research for Prevention
HL	Humeral length
HPA	Hypothalamic-pituitary-adrenal
HPTN	HIV Prevention Trials Network
HR	Hazard ratio
HTLV-III	Human T-cell leukemia virus type-III
IAS	International AIDS Society Conference on HIV Science
ICD-10	International classification of diseases-10th revision
IDU	Injection drug user
IDV	Indinavir
IGF-1	Insulin-like growth factor-1
INSTI	Integrase strand transfer inhibitor
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IOM	Institute of Medicine
IQR	Inter-quartile range
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
IUGR	Intrauterine growth restriction

IV	Intravenous
kg	Kilogram
LAV	Lymphadenopathy-associated virus
LBW	Low birth weight
LGA	Large for gestational age
LMIC	Low and middle-income country
LMP	Last menstrual period
LNMP	Last normal menstrual period
LPV/r	Lopinavir/ritonavir
LTR	Long terminal repeat
MDG	Millennium Development Goal
MICE	Multiple imputation by chained equations
mm	Millimetre
MMR	Maternal mortality ratio
mRNA	Messenger RNA
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
MUAC	Mid-upper arm circumference
MVC	Maraviroc
NBW	Normal birth weight
NCHS	National Center for Health Statistics
Nef	Negative regulatory factor
NFV	Nelfinavir
NHLS	National Health Laboratory Service
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal intensive care unit
NMR	Neonatal mortality rate
NND	Neonatal death
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
NTD	Neural tube defect

NtRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OFD	Occipitofrontal diameter
OR	Odds ratio
OxTREC	University of Oxford Tropical Research Ethics Committee
p7	Protein 7
p11	Protein 11
p17	Protein 17
p24	Protein 24
p32	Protein 32
p51	Protein 51
p66	Protein 66
PAI	Post-attachment inhibitor
PE	Pharmacokinetic enhancer
PGF2α	Prostaglandin F2α
PI	Protease inhibitor
PI	Pulsatility index
PIH	Pregnancy-induced hypertension
PMTCT	Prevention of mother-to-child transmission
Pol	Polymerase
PPROM	Preterm prelabour rupture of membranes
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
PSD	Pediatric Spectrum of HIV Disease
PTB	Preterm birth
RAL	Raltegravir
RCOG	Royal College of Obstetricians & Gynaecologists
RCT	Randomised controlled trial
Rev	Regulator of expression of virion proteins
RNA	Ribonucleic acid

RPV	Rilpivirine
RR	Risk ratio
RTV	Ritonavir
SD	Standard deviation
SDGs	Sustainable Development Goals
SES	Socio-economic status
SFH	Symphysis-fundal height
sFlt-1	Soluble fms-like tyrosine kinase 1
SGA	Small for gestational age
SHAPOSSA	Soweto HIV and ART pregnancy study: the influence of HIV and antiretroviral treatment on pregnancy outcomes in Soweto, South Africa
SIV	Simian immunodeficiency virus
sPTB	Spontaneous preterm birth
SQV	Saquinavir
STI	Sexually transmitted infection
STD	Sexually transmitted disease
sVCAM-1	Soluble vascular cell adhesion molecule 1
sVPTB	Spontaneous very preterm birth
T-20	Enfuvirtide
TAF	Tenofovir alafenamide
Tat	Transactivator of transcription
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TEMPRANO	Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults
Th1	T helper cell 1
Th2	T helper cell 2
TNX-355	Ibalizumab-uiyk
TPV	Tipranavir
UA	Umbilical artery
UK	United Kingdom

UN	United Nations
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
USA	United States of America
UtA	Uterine artery
U=U	Undetectable=Untransmissable
Vif	Viral infectivity factor
VL	Viral load
VLBW	Very low birth weight
Vpr	Viral protein R
VPTB	Very preterm birth
Vpu	Viral protein unique
VSGA	Very small for gestational age
WHO	World Health Organization
ZDV	Zidovudine

Chapter 1: Introduction

The human immunodeficiency virus (HIV) was first discovered in the early 1980s in France and the USA. It is a single-stranded retrovirus of the *Lentivirus* genus of the *Retroviridae* family, and the causative agent for the acquired immunodeficiency syndrome (AIDS). Nearly 70% of the estimated 38 (31.6-44.5) million HIV-positive people worldwide live in sub-Saharan Africa [1]. This region represents 71% of global new HIV infections among women aged ≥15, and 85% among women aged 15-24 [2]. Of the estimated 1.4 million HIV-positive women who become pregnant annually, >90% live in this region [3]. In addition to the HIV epidemic, sub-Saharan Africa has poor perinatal outcomes (e.g. preterm birth [PTB], small for gestational age [SGA] and neonatal death [NND]) [4-7] and the highest fertility rates globally [8,9].

Improvements in antiretroviral therapy (ART) regimens and coverage have changed HIV from a fatal infection to a manageable chronic disease. During the last 20 years, global HIV/AIDS-related deaths have fallen by 51%, shifting from the 8th leading cause of death in 2000 to 19th in 2019. The same figure is seen in low and middle-income countries (LMICs), shifting from 8th to 15th [10]. Among women of reproductive age (15-49 years), AIDS-related deaths decreased by 57%, from 460,000 deaths in 2000 to 200,000 in 2019 [11]. In the context of pregnancy, expansion of ART coverage has partly contributed to a 52% reduction in the global mother-to-child transmission (MTCT) rate between 2010 and 2019, i.e. when 45% and 85% of pregnant women received ART, respectively [3]. The

majority of these women receive lifelong highly active antiretroviral therapy (HAART) initiated before conception [3,12]. However, there is inconsistent evidence as to whether HAART [13-23] and pre-conception initiation of treatment [18,24] are associated with adverse perinatal outcomes. In addition, the safety of *in utero* exposure of certain ART classes, particularly protease inhibitor (PI), remains uncertain [25,26]. Furthermore, the effect of maternal HIV/ART on fetal growth patterns has never been evaluated in any settings, even in high-income countries.

Several factors might have contributed to the above inconsistencies. First, ethical restrictions on the enrolment of pregnant women in most randomised controlled trials (RCTs) of ART [27] result in a reliance on observational evidence, which is prone to bias. Second, small sample sizes and the scarcity of severe outcome events (e.g. stillbirth, very PTB and NND) lead to limited statistical power and biased estimates [17-23]. Third, the use of less accurate methods to estimate gestational and measure birth weight in most existing studies, may result in misclassification of adverse perinatal outcomes. Gestational age is commonly determined using newborn clinical assessment [13], last menstrual period (LMP) [13-17,19,20], symphysis-fundal height (SFH) [13,15,17], and/or late ultrasound [13,15,17,19]. Birth weight is generally measured up to several days after birth or simply captured from medical records [13,14,28-31]. In addition, limited access to ultrasound and delayed first antenatal care (ANC) visits, particularly in sub-Saharan Africa, may have hindered the assessment of fetal growth patterns by maternal HIV/ART status. Given that this assessment requires serial

measurements of fetal biometry throughout pregnancy, low maternal compliance and/or the cost could be other reasons for it not happening.

These suggest the need to conduct studies with accurate gestational age estimation using first trimester ultrasound, serial fetal ultrasound biometry measurements throughout pregnancy and birth weight measurement in a standardised manner within 24h of birth. All are essential to provide better evidence for the effect of maternal HIV/ART on perinatal outcomes and fetal growth patterns, particularly in HIV-endemic settings with high adverse perinatal outcomes and fertility rates, i.e. sub-Saharan Africa. Such studies became even more pertinent by mid-2020 when 185 countries implemented the "treat all" recommendation: immediate initiation of lifelong efavirenz (EFV)-based HAART in all HIV-positive pregnant women irrespective of clinical and immunological status [12,32].

This thesis explores the associations of maternal HIV and ART with eight adverse perinatal outcomes categorised into four groups according to: 1) gestational age at delivery (PTB and very PTB [VPTB]), 2) birth weight (low birth weight [LBW] and very LBW [VLBW]), 3) gestational age at delivery and birth weight (SGA and very SGA [VSGA]) and 4) fetal and neonatal mortality (stillbirth and NND). These associations have been investigated using a systematic review and pairwise meta-analysis of observational studies, and secondary analysis of a prospective longitudinal study with accurate estimations of gestational age and birth weight. The study had previously been conducted at the largest referral hospital in South Africa, a country with the largest HIV epidemic [1] and the highest number of HIV-positive pregnant women receiving lifelong HAART in the world [3].

This thesis is divided into eight chapters, starting with the present Introduction (Chapter 1). Chapter 2 discusses the background to: 1) the association between maternal health and perinatal outcomes; 2) the importance of accurate gestational age estimation, the global burden and consequences of maternal HIV, the perinatal outcomes of interest, and ART in pregnancy, and 3) the relevance of this thesis to HIV-endemic settings, i.e. sub-Saharan Africa.

Chapter 3 explores the effects of maternal HIV/ART, antenatal ART, ART complexity and class, and timing of ART initiation on perinatal outcomes, using a systematic review and pairwise meta-analysis of both unadjusted and adjusted effect estimates of observational studies. Robust sub-group and sensitivity analyses are performed.

Chapter 4 assesses the overlap between measures of perinatal outcomes based on prospectively and accurately determined gestational age and birth weight in both all newborns and HIV-unexposed and HIV-exposed newborns separately. Cohen's kappa (κ) coefficient is estimated to examine the overlap between two perinatal outcomes after taking into account the overlap that would be expected purely by chance.

Chapter 5 evaluates the associations of maternal HIV/ART and timing of ART initiation with the composite outcomes "any adverse perinatal outcome" (stillbirth, PTB, SGA or NND) and "severe adverse perinatal outcome" (stillbirth, VPTB, VSGA or NND).

Chapter 6 evaluates the associations between maternal HIV/ART and specific perinatal outcomes (PTB and SGA), and explores risk factors for PTB and SGA in both all women and HIV-negative and HIV-positive women, separately. Multiple logistic regression is used to control for potential confounders (Chapter 5) or to identify risk factors for PTB and SGA (Chapter 6). Robust analyses are performed: 1) stratified analysis using Mantel-Haenszel method to identify effect modifications; 2) multiple imputation by chained equations to handle missing data and 3) sensitivity analysis to compare the results from complete-case analysis and multiple imputation.

Chapter 7 is the first ever analysis assessing the effect of maternal HIV/ART on fetal growth patterns. Fetal biometric parameters (biparietal diameter, head circumference, abdominal circumference and femur length) measured longitudinally across pregnancy are analysed. The growth trajectories of these fetal biometric parameters are created by fitting linear mixed models, and compared by maternal HIV status and timing of ART initiation.

Chapter 8 summaries the overall findings of this thesis, and provides policy recommendations that have emerged from the present work, including strategies to improve the prediction, prevention, measurement and future research/surveillance of perinatal outcomes.

Chapter 2: Background

2.1 Impact of maternal health on perinatal outcomes

In 2019, almost half (49.6%) of the estimated 7.7 billion global population were female; 50% of women were aged 15–49 years and nearly 5% 12–14 years [8,33]. Approximately 210 million pregnancies and 140 million live births occur annually [34]; therefore, maternal health is not a minor issue. It is a pre-condition and a determinant of perinatal, child and adolescent health.

An integrated perinatal health framework illustrating how maternal health influences pregnancy and perinatal outcomes was first proposed by Misra et al. [35]. The framework integrates two approaches: “life course” (Figure 2.1) and “multiple determinants” (Figure 2.2). The life course approach emphasizes that both pre-conception and inter-conception (between pregnancies) periods should be considered as targets for interventions aimed at improving maternal and perinatal health [35]. The pre-conception period begins with childhood and ends either with menopause or the first pregnancy (Figure 2.1). The rationale for this approach is that several powerful determinants of perinatal outcomes are related to maternal risk factors occurring long before conception [35]. For example, longitudinal studies [36,37] have shown that adults’ nutritional status is influenced by childhood lifestyle, physical activity and dietary intake.

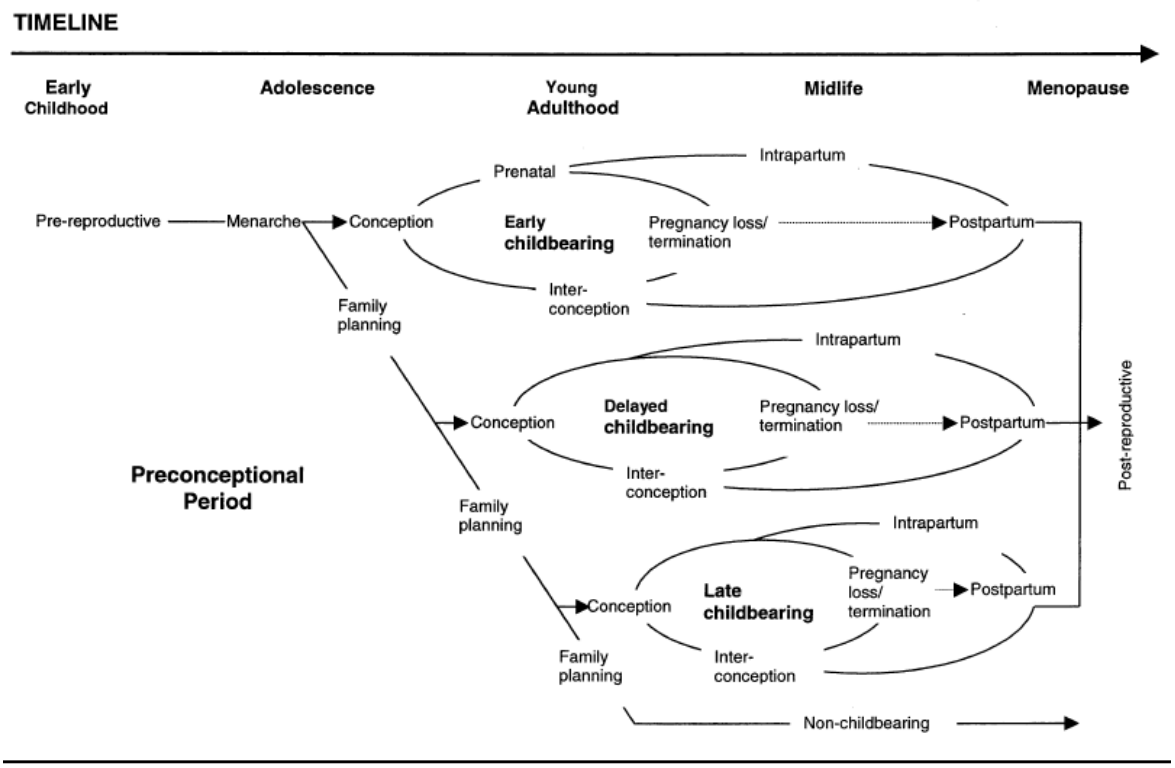


Figure 2.1. Women's reproductive cycle (Misra et al. [35]).

The multiple determinants approach suggests that maternal health is a multifactorial condition influenced by proximal and distal determinants [35] (Figure 2.2). Distal determinants include genetic factors (e.g. gene-environment interaction), physical (e.g. air pollution) and the social milieu (e.g. socio-economic status) (Figure 2.2), all of which may influence a woman's health directly. However, they are more relevant in increasing or decreasing a woman's susceptibility to proximal determinants [35]. These include biomedical, i.e. any co-existing health condition (e.g. infection) and behavioural factors, i.e. both high-risk and protective behaviours the woman admits to (e.g. smoking) [35] (Figure 2.2).

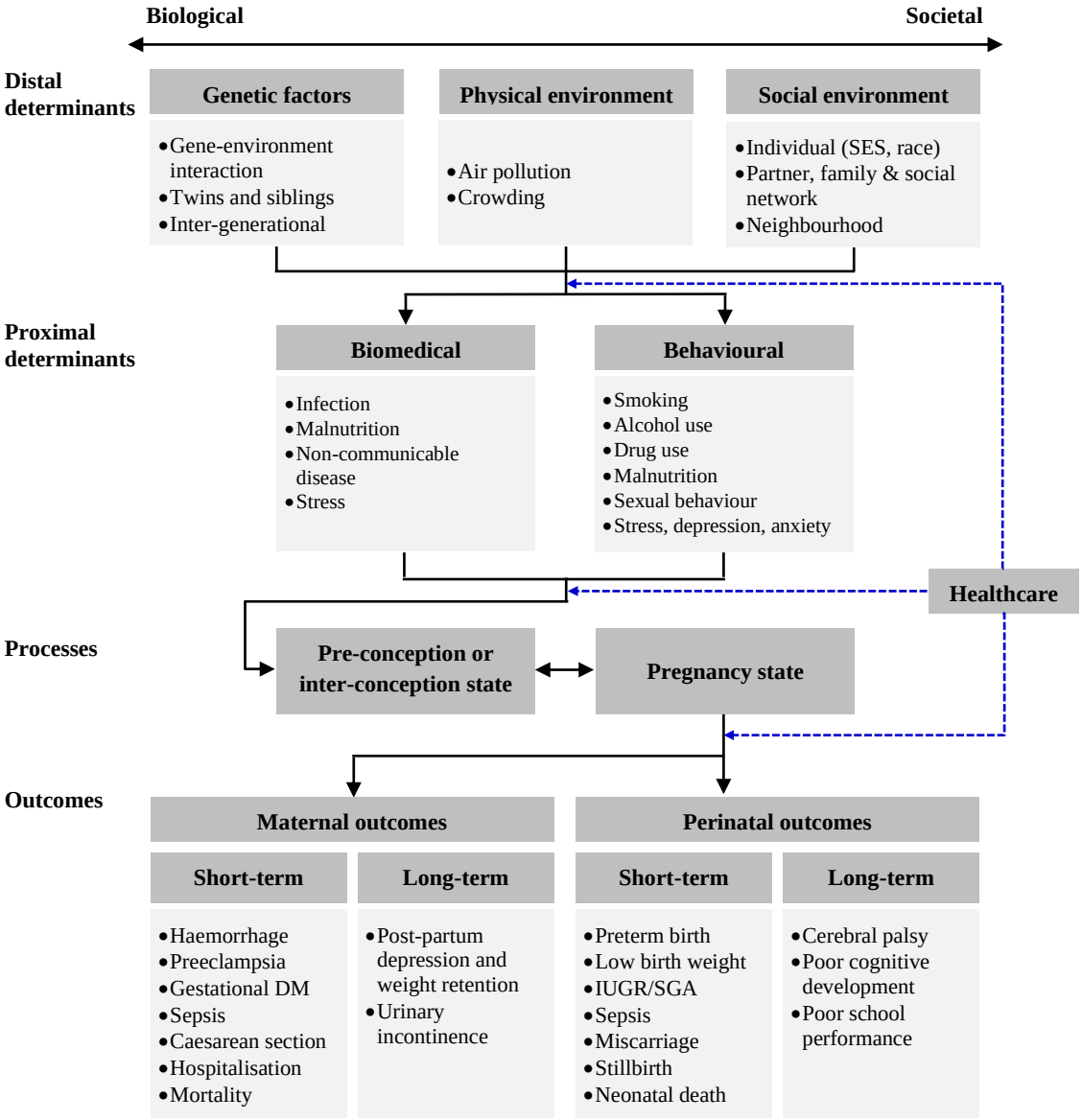


Figure 2.2. Multiple determinants framework for maternal and perinatal health. Adapted from Misra et al. [35]. Abbreviations: DM, diabetes mellitus; IUGR, intrauterine growth restriction; SES, socio-economic status; SGA, small for gestational age.

The influence of distal determinants occurs throughout the woman's reproductive life, suggesting these are very difficult to address using perinatal interventions alone. Proximal determinants may influence maternal health independently or through inter-relationships between them [35]. For example, women who smoke or consume alcohol or illicit drugs are more likely to have risky sexual behaviours [38-41]. These have been shown to be associated with sexually transmitted

infections (e.g. HIV infection) [38,41,42] and non-communicable diseases (e.g. hypertension and obesity) [43-45]. Infectious and non-communicable diseases aggravated by risky behaviours will compromise maternal health during both the pre-conception and inter-conception periods. Changes and demands during pregnancy will exacerbate poor maternal health; without proper interventions, this will result in poor maternal and infant outcomes. These highlight the importance of proximal factors as targets for perinatal interventions [35].

The framework includes short- and long-term outcomes for both the mother and infant (Figure 2.2). The short-term outcomes for the mother include haemorrhage, preeclampsia, gestational diabetes, sepsis, Caesarean section, antenatal hospitalisation and mortality; the long-term outcomes include post-partum depression, weight retention and urinary incontinence. The short-term outcomes for the infant include preterm birth (PTB), low birth weight (LBW), intrauterine growth restriction (IUGR)/small for gestational age (SGA), congenital malformation, sepsis, miscarriage, stillbirth and neonatal death (NND); the long-term outcomes include cerebral palsy, poor cognitive development and school performance, reduced earning potential and loss of productivity [35].

The framework also includes health care, defined as any strategies from primary prevention to medical interventions (Figure 2.2). Good health systems with adequate access to services implementing evidence-based clinical practice with sufficient skilled staff, equipment, supplies and drugs can modify the relationships among components within the framework, and improve maternal and infant

outcomes [35,46]. Health systems and care providers should ensure that high-quality and evidence-based care are accessible for all women in a timely manner.

2.2 Epidemiology

2.2.1 Maternal health

Maternal mortality is an indicator of overall maternal health, the quality of reproductive health care, the general health of the population and the progress of international development goals [47]. Despite improvements in the past 27 years (1990–2017), preventable maternal deaths related to pregnancy or childbirth are still high with an estimated 295,000 deaths worldwide in 2017 [48,49]. The vast majority (94%) of these deaths occur in low and middle-income countries (LMICs) [50]. Sub-Saharan Africa and south Asia account for approximately 86% (254,000) of the global maternal deaths [48]. The 2017 global maternal mortality ratio (MMR) was estimated at 211 per 100,000 live births [48] – a 67% decrease is needed to achieve the ambitious target of the Sustainable Development Goal (SDG) 3.1: global MMR <70 per 100,000 live births by 2030 [51]. Sub-Saharan Africa was the only region with very high MMR in 2017: 542 per 100,000 live births [48].

Table 2.1 shows the global distribution of causes of maternal deaths using the World Health Organization (WHO) systematic analyses, comparing the 1997-2002 [52] with 2003-2009 data [53]. The major direct obstetric causes accounting for nearly 80% of all maternal deaths between 1997 and 2002 were haemorrhage (31.1%), hypertensive disorders (17.9%), obstructed labour (10.9%), sepsis/infections (10.9%) and unsafe abortion (9.1%) [52] (Table 2.1). These

direct causes were consistently responsible for the majority of maternal deaths between 2003 and 2009 [53] (Table 2.1). All direct causes (with the exception of embolism) appear to have decreased over time (Table 2.1); the largest decrease was obstructed labour (8.1%), and the smallest was sepsis/infections (0.2%) [52,53]. However, these findings differed from the Global Burden of Disease (GBD) study [54], which showed: 1) 3% and 1% increases in the proportions of maternal deaths due to abortive outcomes and hypertensive disorders, respectively and 2) a modest decrease (1%) in obstructed labour between 1990 and 2013. The latest GBD study [55] estimated that 72.2% of maternal deaths worldwide in 2017 were attributed to direct obstetric complications: haemorrhage (23.3%), hypertensive disorders (17.8%), sepsis/infections (12.8%), unsafe abortion (10.3%) and obstructed labour (8%) (Figure 2.3).

Table 2.1. Causes of maternal deaths in 2002 and 2009.

Causes of maternal deaths	**Distribution of causes of maternal deaths (%)**	
	1997–2002[§]	**2003–2009[ǀ]**
Abortion	9.1	7.9
Embolism	2.1	3.2
Haemorrhage	31.1	27.1
Hypertensive disorders	17.9	14.0
Obstructed labour	10.9	2.8
Sepsis/infections	10.9	10.7
Other direct causes	5.9	6.8
HIV-related	Africa: 6.2	5.5
Other indirect causes	12.1	22.0

[§] Khan et al. [52].
[ǀ] Say et al. [53].
Abbreviation: HIV, human immunodeficiency virus.

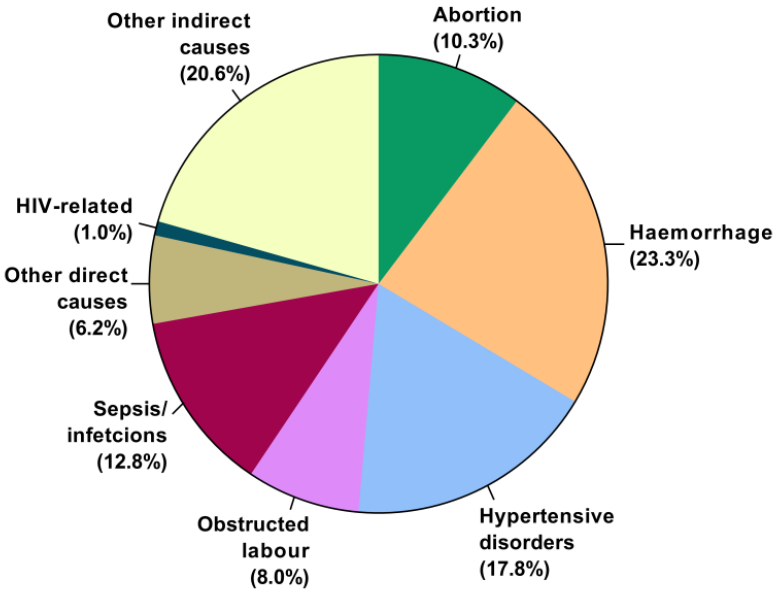


Figure 2.3. Percentage distribution of causes of maternal deaths in 2017. Data source: GBD 2017 Causes of Death Collaborators [55]. Abbreviations: GBD, Global Burden of Disease; HIV, human immunodeficiency virus.

Regarding indirect causes, the proportion of global HIV-related indirect maternal deaths in 2002 could not be estimated from the WHO data [52] because this information was available for Africa only (6.2%) (Table 2.1). The effect of HIV on maternal deaths appears to be less pronounced over time: 5.5% of all maternal deaths in 2009 [53] versus 1.2% in 2017 were attributed to HIV [48] (Figure 2.4). However, these results differed from those reported by the GBD studies: 0.2% of maternal deaths in 1990 were due to HIV, which rose to 1% in 2013 [54] and then leveled off in 2017 [55] (Figure 2.4). Sub-Saharan Africa accounts for the largest proportion of global HIV-related indirect maternal deaths: 84,000 of 134,000 (63%) deaths in 2009 [53] and 3,200 of 3,600 (89%) in 2017 [48]. In 2009, WHO estimated that 6.4% of all maternal deaths in sub-Saharan Africa were HIV-related [53], and this estimate dropped considerably to 1.6% in 2017 [48].

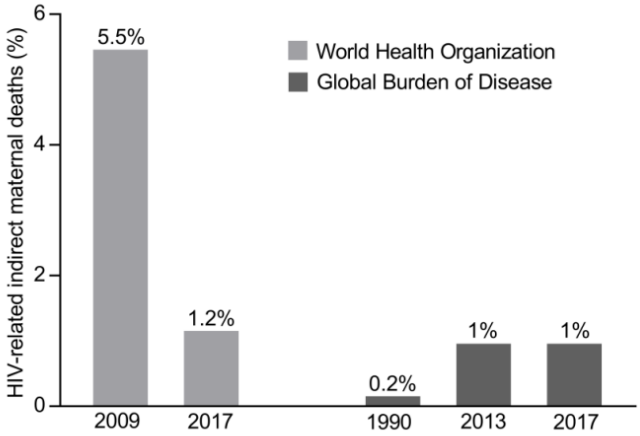


Figure 2.4. Percentage of HIV-related indirect maternal deaths according to the WHO and GBD. Data source: Say et al. [53], WHO 2019 [48], and GBD 2013 and 2017 Causes of Death Collaborators [54,55]. Abbreviations: GBD, Global Burden of Disease; HIV, human immunodeficiency virus; WHO, World Health Organization.

The notable decline in HIV-related maternal deaths reflects the improved care and management of HIV disease, particularly during pregnancy. The use of antenatal antiretroviral therapy (ART) to improve maternal health and prevent vertical HIV transmission has been one of the most successful global public health programmes in the last decade. Between 2004 and 2015, lifelong ART was only indicated for HIV-positive pregnant women who met immunological (CD4 ≤200 or ≤350 cells/μL) or clinical criteria (HIV stage 3 or 4) [56-59]. Since 2016, the "treat all" recommendation has suggested an immediate initiation of lifelong ART for all HIV-positive pregnant women irrespective of immunological and clinical status [12]. The clear benefits of antenatal ART for improving maternal health and reducing HIV-related maternal deaths and paediatric HIV infections worldwide [11,60] has led to a rapid increase in the global landscape of antenatal ART coverage [61] (Figure 2.5). In 2019, 85% of pregnant women worldwide (Figure 2.5) – corresponding to 1.1 million women – received antenatal ART, 92% of whom were living in sub-Saharan Africa [61].

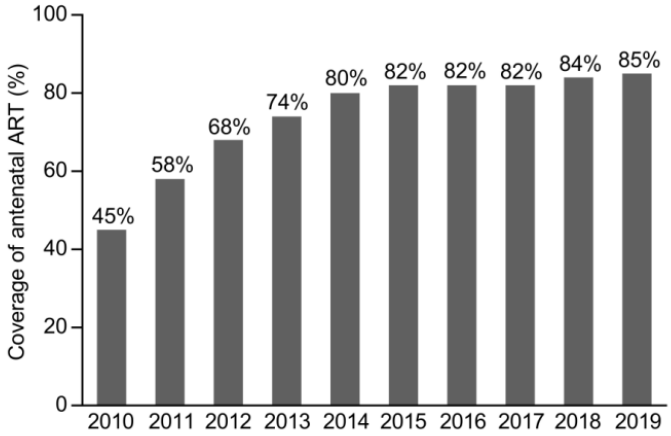


Figure 2.5. Global coverage of pregnant women receiving antiretroviral therapy. Data source: UNAIDS 2020 [61]. Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

Concerns have been raised about the safety of ART in pregnancy, including an increased risk of adverse perinatal outcomes [62-64], as well as cancer [65,66] and growth problems in childhood [67]. In addition, HIV-exposed uninfected children have increased morbidity and mortality compared with HIV-unexposed children [68,69]. Despite the multifactorial determinants of this increased mortality, *in utero* ART exposure may be a contributing factor.

2.2.2 Perinatal health

According to articles 6 and 24 of the Convention on the Rights of the Child, all newborns have a right to the highest attainable standard of health and health care, and WHO Member States have a responsibility to reduce infant and child mortality [70]. However, these rights are not fully protected, particularly for newborns in LMICs. Despite an impressive 50% reduction in NND (i.e. newborn death in the first 28 days of life) since 1990, nearly 2.5 million NNDs were reported in 2019, accounting for 47% of under-5 deaths; more than two million

were also stillborn [4,71,72]. Almost all NNDs (98%) occur in LMICs; sub-Saharan Africa and south Asia account for 80% of the global NNDs [4,5,71]. In 2019, the highest neonatal mortality rate (NMR) – 27 per 1,000 live births – was reported in sub-Saharan Africa [4]. Of the 10 countries with the highest NMRs, eight were in this region [5].

Approximately 75% of NNDs occur during the first week of life, with 33% on the day of birth [4,5]. The four main causes of NNDs include PTB complications, intrapartum-related deaths, neonatal infections and congenital abnormalities [4,73]. PTB, SGA, or both are the greatest risk factors for more than 80% of NNDs in sub-Saharan Africa and south Asia [74]. In addition, surviving PTB babies have higher risks for post-neonatal mortality, long-term neurological and sensory deficits, stunting and adult-onset non-communicable diseases; SGA babies have higher risks for stunting and adult-onset metabolic conditions [5,74,75]. Furthermore, in 2019, neonatal disorders (e.g. PTB) were the first leading cause of global disability-adjusted life-years (DALYs), especially for children <10 years old [75]. These adverse perinatal outcomes could have detrimental effects, including loss of human potential for lifelong health and well-being, long-term psychological and financial problems for family members of affected newborns, and, in turn, restrictions on a country's economic and social development [5].

In order to achieve the SDG 3.2 target: global NMR ≤12 per 1,000 live births, and to end preventable stillbirths ≤12 per 1,000 total births by 2030, WHO and the United Nations Children's Fund (UNICEF) have proposed the Every Newborn

Action Plan encompassing five strategic objectives. One of these objectives highlights the importance of accurate gestational age estimation to improve the epidemiology of PTB and SGA and the comparability of neonatal mortality estimates stratified by gestational age [5,51,72].

2.3 Determination of gestational age

Neonatal mortality is a relatively rare event. Therefore, more prevalent proxies – e.g. PTB and SGA – have been used to monitor progress or to observe an effect of a public health intervention on reducing neonatal mortality. In the context of newborn health, estimating gestational age accurately is essential for identifying PTB and SGA newborns, and providing them with effective interventions [76,77]. WHO recommends ultrasound scan <24 weeks to estimate gestational age [78]. Whereas, according to the American College of Obstetricians and Gynecologists (ACOG), first-trimester (<14 weeks' gestation) ultrasound measurement of crown-rump length (CRL) is the most accurate method to determine gestational age [79] as biological variation in fetal size is minimal in this period [80]. However, accurate gestational age estimation has been lacking in sub-Saharan Africa and south Asia, where the vast majority of PTB and SGA babies are born [6,7]. This is partly due to limited ultrasound availability in these regions: in sub-Saharan Africa <7% of pregnant women have access to antenatal ultrasound. Another reason is that the first antenatal care (ANC) visit is typically delayed until late in the second trimester [7,81-84]. In the context of research, almost no sub-Saharan African studies to date, particularly in HIV-endemic settings, have used first-trimester ultrasound to confirm gestational age. The most common methods

used in this region include newborn clinical assessment [13], the first day of the last menstrual period (LMP) [13-17], symphysis-fundal height (SFH), and/or late ultrasound [13,15,17].

Newborn clinical assessment is challenging in LMICs due to 1) high rates of SGA, which may influence the assessment of newborn maturity, and 2) delayed first newborn contact and inadequate lighting for home births [77,85,86]. A systematic review has shown that newborn clinical assessments tend to overestimate gestational age and so lead to PTB misclassification. Conversely, they tend to underestimate gestational age among SGA babies [77].

LMP also has several limitations: 1) it is often poorly recalled or unknown – 67% of women in LMICs, particularly younger, primiparous and illiterate women, do not have a recorded LMP; 2) irregular menstrual cycles; 3) the day of ovulation may vary cycle-to-cycle, and 4) misinterpretation of early pregnancy bleeding [76,77,82,84,87-89]. On average, LMP tends to overestimate gestational age compared with first-trimester ultrasound [88].

Whilst SFH measurement is simple, inexpensive and routinely performed in almost all antenatal settings worldwide, not all pregnancies benefit from SFH as a mean of estimating gestational age due to: 1) body mass index (BMI) >35 kg/m^2; 2) maternal morbidities (e.g. uterine fibroids), and 3) the high risk of IUGR, i.e. SFH measurement is more challenging in settings with high SGA rates [84,89-91]. Other factors, such as maternal parity and nutrition, may also influence the accuracy of SFH [84]. Longitudinal SFH measurements – up to six measurements – have been shown to improve gestational age estimation compared with single

measurement [84,90,92]; however, this seems difficult in LMICs with low rates of sequential ANC visits [84,93].

Given the normal biological variation in fetal size and the possibility of IUGR, second and third trimester ultrasound scans are less reliable than first-trimester ultrasound for gestational age estimation, and they become increasingly inaccurate as gestation advances [84,89,94,95]. Furthermore, variations in fetal skull shape (dolichocephaly, brachycephaly), fetal body position and abnormalities (aneuploidy, skeletal dysplasia) may influence biometric measurements in the second and third trimester [89]. The WHO AMANHI Study Group [94] has shown that a novel parsimonious model formula combining fetal transcerebellar diameter with femur length could improve the accuracy of late (>24 weeks' gestation) ultrasound scans in estimating gestational age in LMICs (Bangladesh, Pakistan and Tanzania), within approximately ±2 weeks of the gold-standard CRL measurement. Whilst this is a notable achievement in resource-limited settings where access to the first-trimester scan is lacking, a concern about the validation of this finding in other LMIC populations has been raised [95].

The above-mentioned factors conspire to make it difficult to estimate gestational age accurately based on non-first-trimester CRL measurement. At individual level, this may mislead clinical decision-making (e.g. the provision of antenatal corticosteroids and timing of labour induction), or delay the recognition of PTB and SGA babies requiring life-saving interventions [7,84]. At population level, this may lead to biased estimates of PTB and SGA rates and epidemiological associations with these adverse perinatal outcomes. For example, less accurate

gestational age estimation might have partly contributed to inconsistent findings for the associations of treated maternal HIV infection with PTB and SGA among sub-Saharan African studies [14,28,29,96,97]. As another example, antenatal corticosteroids are recommended for women in threatened pre-term labour from 24 to 34 weeks' gestation to improve newborn outcomes [98,99]. However, the Antenatal Corticosteroids Trial [100] was unable to show the benefits of the medication among infants $<5^{th}$ centile for birth weight; instead it was associated with an overall increase in NND and stillbirth, and higher rates of suspected maternal infection. The authors considered inaccurate gestational age estimation, resulting in treatment outside the optimal window for intervention, as a potential reason for these findings [100].

2.4 The present DPhil work

The triple impact of maternal HIV/ART, poor perinatal outcomes and high fertility in sub-Saharan Africa is clear. Approximately 92% of 1.4 million HIV-positive women becoming pregnant every year reside in sub-Saharan Africa [101]; and the vast majority of them receive lifelong ART [61]. Furthermore, sub-Saharan Africa and south Asia account for approximately 80% of global NNDs [4,5], 81% of PTBs [6] and 78% of SGAs [7]. In addition, sub-Saharan Africa has been forecasted to have the highest fertility rates globally until 2100 [8,9]. Of the 25 countries with the highest fertility rates, 23 are in this region [8]. Lack of ultrasound and delayed first ANC visit are also major issues in sub-Saharan Africa, which have limited the practice of first-trimester CRL measurement – the most accurate method for dating a pregnancy [79].

With regard to the perinatal health framework proposed by Misra et al. [35] (Figures 2.1 and 2.2), the present DPhil work focuses on several points:

1. Treated maternal HIV infection as a proximal factor.
2. Adverse perinatal outcomes (e.g. PTB, SGA) and fetal growth patterns as short-term infant/fetal outcomes.
3. The present work was based on a prospective pregnancy cohort study conducted in South Africa, a country with the highest numbers of HIV-positive people and HIV-positive pregnant women on ART in the world. All participating women were accurately dated using first-trimester ultrasound.

2.5 Maternal HIV infection

2.5.1 History and origin of HIV/AIDS

In 1981, a new disease of severe immunodeficiency characterised by rare opportunistic infections (e.g. Pneumocystis pneumonia) and malignancies (Kaposi's sarcoma) was firstly recognised among gay men in the USA [102-104]. In 1982, the term "acquired immunodeficiency syndrome" (AIDS) was first used by the Centers for Disease Control and Prevention (CDC) to describe the disease [105]. In Uganda, this new disease was locally known as "slim disease", with major symptoms of weight loss and diarrhoea [106]. In 1983, CDC reported that two women developed immunodeficiency during a close relationship with men who had AIDS, suggesting that the disease could be transmitted via heterosexual intercourse [107]. Furthermore, 21 infants with unexplained immunodeficiency were also reported, suggesting vertical transmission before, during, or shortly after birth [108]. A new retrovirus called lymphadenopathy-associated virus

(LAV) that could be the cause of AIDS was discovered in France [109]. In 1984, the identical retrovirus called human T-cell leukemia virus type-III (HTLV-III) was discovered in the USA [110]. In 1986, the International Committee on Taxonomy of Viruses announced the official name of AIDS virus: human immunodeficiency virus (HIV). Zidovudine was the first ART approved by the US Food and Drug Administration (FDA) in 1987 [111]. In 1994, the Pediatric AIDS Clinical Trials Group showed that antenatal zidovudine reduced the risk of mother-to-child transmission (MTCT) by approximately 67.5% [112]. Since then, antenatal ART has been recommended to improve maternal health and prevent MTCT [113]. Other key historical events of HIV/AIDS between 1981 and 2019 are provided in Appendix 2.1: Table 2.1.

Two types of HIV (HIV-1 and HIV-2) are the result of cross-species transmissions of other immunodeficiency viruses, which naturally infect African monkeys and apes and are collectively named simian immunodeficiency viruses (SIVs) with a suffix indicating their species of origin [114,115] (Figure 2.6). For example, SIVsmm denotes SIV from sooty mangabey, SIVcpz from chimpanzee and SIVgor from gorilla (Figure 2.6). The origin of HIV-2 was determined first. HIV-2 was identified in 1986 as a causative agent of AIDS among patients in West Africa. HIV-2 was distantly related to HIV-1 but closely related to SIV infecting sooty mangabey (SIVmm) (Figure 2.6). In 1989, sooty mangabey was proposed as the source of HIV-2 [114,115]. There are eight groups of HIV-2 (A to H), but only groups A and B have spread amongst humans, particularly in West Africa. Figure 2.6 shows that the origin of HIV-1 is chimpanzee, the natural reservoir for SIVcpz. HIV-1 encompasses four groups: major (M), non-major and

non-outlier (N), outlier (O) and putative (P); each group represents a unique cross-species transmission event (Figure 2.6). Groups N, O and P are largely restricted to Cameroon, Gabon and neighbouring countries, and represent only ±2% of the global HIV prevalence [115,116]. Group M is responsible for the global HIV epidemic, accounting for approximately 97% of all HIV infections [116].

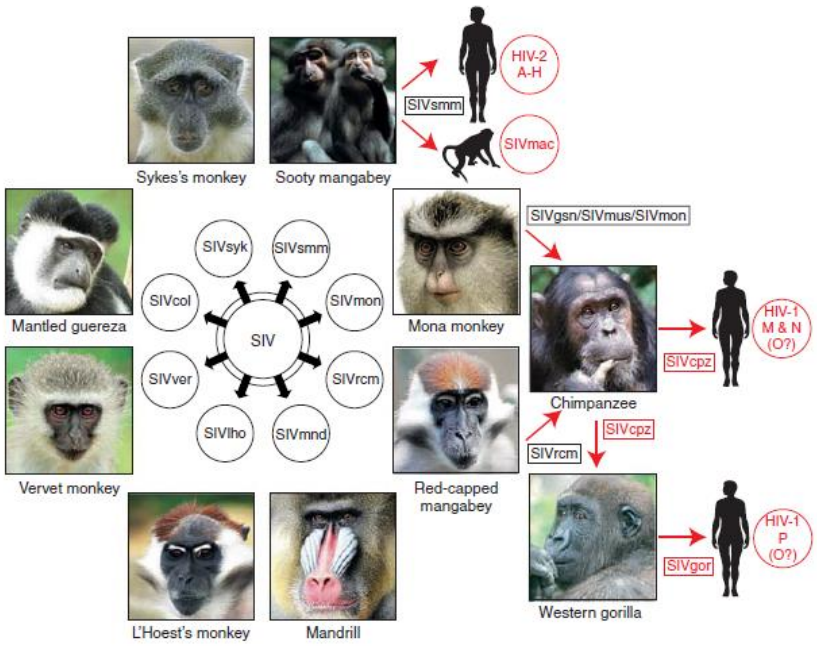


Figure 2.6. Origins of HIV-1 and HIV-2, see text (Sharp et al. [115]). Red indicates examples of cross-species transmissions and the resulting viruses. Abbreviations: HIV, human immunodeficiency virus; SIV, simian immunodeficiency virus.

2.5.2 HIV-1 molecular structure and replication cycle

HIV is a member of the *Lentivirus* genus of the *Retroviridae* family. The mature HIV-1 virion is spherically shaped and approximately 100-120nm in diameter (Figure 2.7). The outer part of the virus is composed of a lipid-bilayer membrane in which are embedded the viral envelope glycoproteins gp120 and gp41. Underneath, and attached to, the lipid-bilayer membrane is a spherical protein composed of the matrix protein. The core of the mature HIV-1 is a capsid protein

containing viral enzymes reverse transcriptase and integrase and the nucleocapsid protein complexed with dimerized viral genomic RNA [117-122] (Figure 2.7).

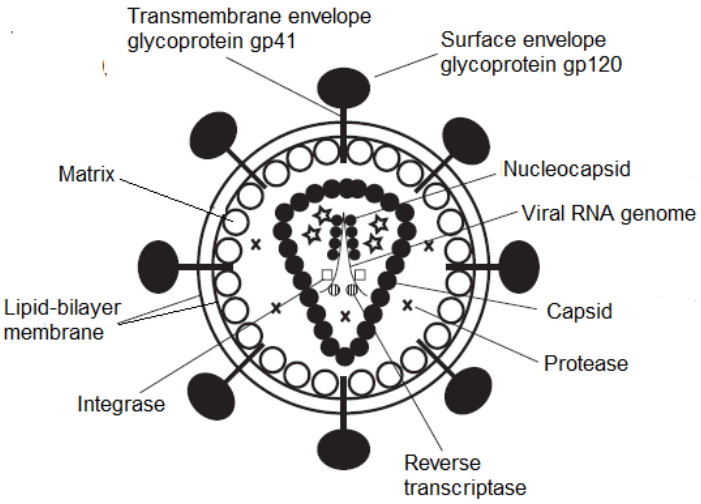


Figure 2.7. Structure of a mature HIV-1 virion. Adapted from Adamson et al. [120]. Abbreviations: HIV, human immunodeficiency virus; RNA, ribonucleic acid.

The HIV-1 genome (Figure 2.8) is characterised by the presence of three major genes: *gag*, *pol* and *env*, which are common to all retroviruses. The *gag* gene encodes the structural proteins of matrix (p17), capsid (p24) and nucleocapsid (p7). The *pol* gene encodes enzymatic proteins required for reverse transcription (reverse transcriptase, p66/p51), integration (integrase, p32) and proteolytic processing of viral proteins (protease, p11). The *env* gene encodes a glycoprotein precursor gp160, which is cleaved to the surface envelope glycoprotein gp120 and transmembrane glycoprotein gp41 [117-122]. The HIV-1 genome also contains regulatory genes: *tat* and *rev*, and accessory genes: *vif*, *vpr*, *vpu* and *nef* [118,119,121,122], which seem important in the viral life cycle although their precise roles are not entirely understood (Appendix 2.2: Table 2.2).

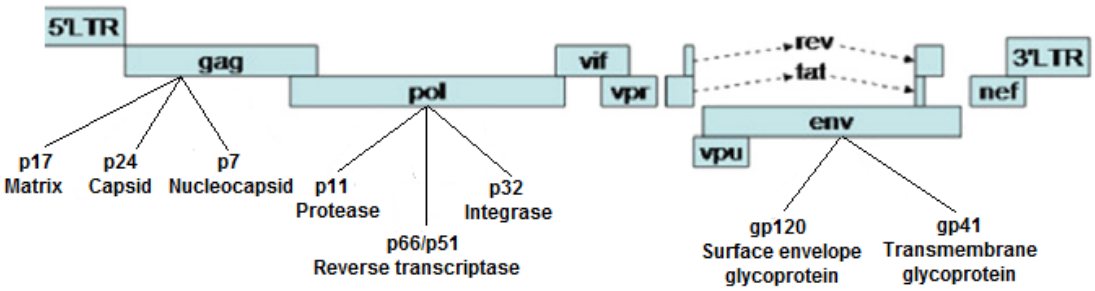


Figure 2.8. Structure of the HIV-1 genome. Adapted from Teixeira et al. [118]. Abbreviations: HIV, human immunodeficiency virus; LTR, long terminal repeat.

Figure 2.9 shows a schematic overview of the HIV-1 replication cycle. Step 1 is the entry of HIV-1 into a host cell involving three key steps: 1) the binding of HIV-1 gp120 to the host CD4 receptor; 2) the gp120-CD4 receptor complex interacts with a coreceptor (chemokine CCR5 or CXCR4) on the host cell surface, and 3) HIV-1 gp41 mediates fusion of HIV-1 with the host surface membrane to permit viral entry. Step 2 is reverse transcription: the single-stranded HIV-1 RNA is transcribed into double-stranded DNA by the viral enzyme reverse transcriptase. Step 3 is the migration of newly synthesised viral DNA into the host nucleus and its integration into the host DNA by the viral enzyme integrase. Step 4 is the transcription of HIV-1 DNA into messenger RNA (mRNA) and genomic RNA. Step 5 is the transport of HIV-1 RNA outside the host nucleus and the translation of HIV-1 mRNA into viral proteins. Step 6 is the cleavage of these transcribed proteins into smaller proteins by the viral enzyme protease. Step 7 is the assembly of a new virus particle containing viral genomic RNA and enzymes (reverse transcriptase, integrase and protease). Step 8 is the budding, release and maturation of a new virus particle [118,119,121,123-125].

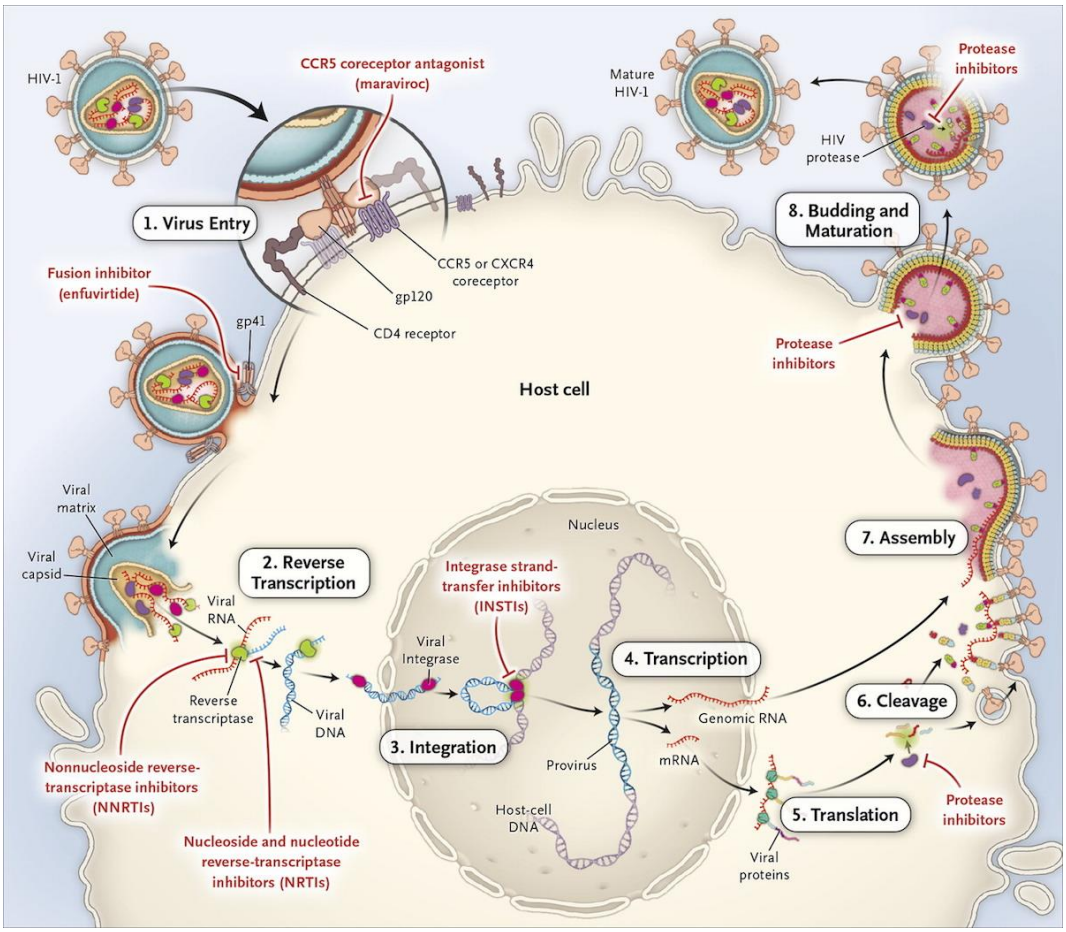


Figure 2.9. HIV-1 replication cycle (Gandhi et al. [123]). Abbreviations: DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; mRNA, messenger RNA; RNA, ribonucleic acid.

2.5.3 HIV-1 transmission

The routes of HIV-1 transmission include sexual contact across mucosal surfaces, percutaneous inoculation, and MTCT or vertical transmission. Unprotected heterosexual contact is responsible for nearly 70% of new HIV-1 infections worldwide; the remainder are largely associated with men who have sex with men (MSM), MTCT and injection drug use [126] (Table 2.2).

Table 2.2. HIV-1 transmission routes and per-contact risks.

HIV invasion site	Anatomical sublocation	Transmission medium	Per-contact transmission probability	Estimated contribution to global HIV cases
Female genital tract	Vagina, cervix	Semen, blood	1 in 200 to 1 in 2,000	12.6 million
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions, blood	1 in 700 to 1 in 3,000	10.2 million[§]
Intestinal tract	Rectum	Semen, blood	1 in 20 to 1 in 300	3.9 million[ǀ]
	Upper gastrointestinal tract	Semen, blood	1 in 2,500	1.5 million
		Maternal blood, genital secretions (intrapartum)	1 in 5 to 1 in 10	960,000[¥]
		Breast milk	1 in 5 to 1 in 10	960,000[¥]
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20	480,000[¥]
Bloodstream	–	Blood products, sharps	95 in 100 to 1 in 150	2.6 million[¶]

[§] Includes men who have sex with men (MSM), and bisexual and heterosexual men.
[ǀ] Includes MSM, bisexual men, and women infected via anal receptive intercourse.
[¥] Mother-to-child transmission.
[¶] Mostly intravenous drug use, but includes infections by transfusions and health-care-related accidents.
Adapted from Shaw et al. [126].

2.5.3.1 Sexual transmission

Despite the varied estimated risk of sexual HIV transmission (Table 2.2), existing studies have consistently shown an increased risk associated with: 1) anal compared with vaginal intercourse, and 2) receptive compared with insertive intercourse [126-129]. Rectal mucosa is more susceptible to abrasions than vaginal mucosa due to a higher density of lymphoid follicles, i.e. HIV target cells [130,131]. The per-contact risk estimates of HIV transmission from unprotected anal intercourse range from 0.06% to 1.70%; by type of anal intercourse: receptive 0.50% to 1.70% and insertive 0.06% to 0.16% [132-136] (Appendix 2.2: Table 2.3). The risk of HIV transmission via anal intercourse is comparable between heterosexual and MSM couples [132]. The per-contact risk estimates of

HIV transmission through vaginal intercourse range from 0.05% to 0.19%; by type of vaginal intercourse: receptive 0.08% to 0.19% and insertive 0.05% to 0.1% [133,134,137] (Appendix 2.2: Table 2.4).

2.5.3.2 Percutaneous inoculation

Among injection drug users (IDUs) or health workers (via accidental percutaneous exposure), per-injection risk estimates of HIV transmission from a contaminated needle and syringe range from 0.23% to 0.84% [138-142] (Appendix 2.2: Table 2.5). In addition, prospective cohorts of IDUs have shown that sharing needles and syringes with people with unknown HIV status is associated with an increased risk of HIV transmission: adjusted hazard ratios 1.48 to 3.03 [143-146] (Appendix 2.2: Table 2.6).

2.5.3.3 Mother-to-child (MTCT) or vertical transmission

The routes of MTCT include *in utero* transmission, exposure to maternal blood and genital tract secretions during labour and delivery, and post-natal transmission via breastfeeding [147]. Before the introduction of highly active antiretroviral therapy (HAART), MTCT rates were up to >42% [148-150]; after the introduction HAART, the rates have been <2% [17,151-156] (Appendix 2.2: Table 2.7).

2.5.3.4 Co-factors influencing the risk of HIV transmission

The varied estimated risks of HIV transmission, as shown above, are in part attributed to differences in the prevalence of several co-factors across populations studied:

1. **Viral load (VL).** For sexual HIV transmission, VL probably serves as a surrogate for HIV concentrations in genital secretions [157,158]. Each $\log_{10}$ increase in plasma VL increases the per-act risk of sexual HIV transmission by 2.5 to 2.9-fold [137,159]. For MTCT, the rates of transmission increase with corresponding increases in maternal VL [160,161]. Every $\log_{10}$ increase in maternal VL increases the risk of MTCT by nearly two-fold [161].
2. **Sexually transmitted infections (STIs),** which promote sexual HIV transmission by increasing both the susceptibility to [162-171] and the infectiousness of HIV [164,170-173]. The mechanisms through which STIs increase the risk of MTCT remain unclear. Several hypotheses have been proposed: increased genital shedding of HIV, local inflammation and VL [174]. Co-infection with STIs nearly doubles MTCT risk [175].
3. **Stage of HIV disease**. Primary or acute stage has the highest transmissibility, particularly for sexual HIV transmission. During the acute stage, immune responses have not yet been developed, resulting in a high degree of viral replication, and an increased VL in plasma and genital secretions [176]. In addition, the acute stage is associated with a high prevalence of concomitant STIs and lack of awareness of HIV seroconversion [177].
4. **Circumcision**, which has been associated with an approximately 50% reduced risk of female-to-male sexual HIV transmission [178,179].
5. **Mode of delivery**. Pre-HAART evidence suggests that elective Caesarean section reduces MTCT risk by 50% to 80% [180,181]. However, among women receiving HAART, MTCT rates are comparable between vaginal and Caesarean deliveries [182].

6. **Pregnancy-related events**, such as ruptured membranes. A meta-analysis has shown that the risk of MTCT increases by approximately 2% for each 1h increment in the duration of ruptured membranes [183].
7. **Other behavioural co-factors**, e.g. type of sexual partner (main or casual) [177,184] and genital piercing for sexual HIV transmission [185]; maternal smoking and illicit drug use, which have been associated with pregnancy complications (including premature rupture of membranes) that, in turn, are associated with a higher MTCT risk [186].

2.5.4 HIV-1 natural history and immunopathogenesis

More than 80% of adult HIV-1 infections are transmitted through the exposure of mucosal surface to the virus, predominantly via a heterosexual route [187-189]. Figure 2.10 shows the three ways HIV-1 crosses the cervicovaginal mucosal barrier in heterosexual transmission: 1) by infection of dendritic cells, 2) transcytosis (cell-free virus), or 3) infection of intraepithelial lymphocytes. After crossing the mucosal barrier, HIV-1 infects dendritic cells, resting and activated $CD4^+$ T cells and macrophages in the underlying sub-mucosa. Infection is subsequently disseminated to the draining lymph nodes that spread infection to other organs and peripheral tissues [188,190-194]. As these initial events occur in the sub-mucosa and lymphoid system, the virus cannot be detected in plasma – the so-called eclipse stage, lasting 7 to 21 days [187,190,191]. The progression of HIV-1 infection can be described in three stages: acute, asymptomatic and AIDS [188,190-194] (Figure 2.11).

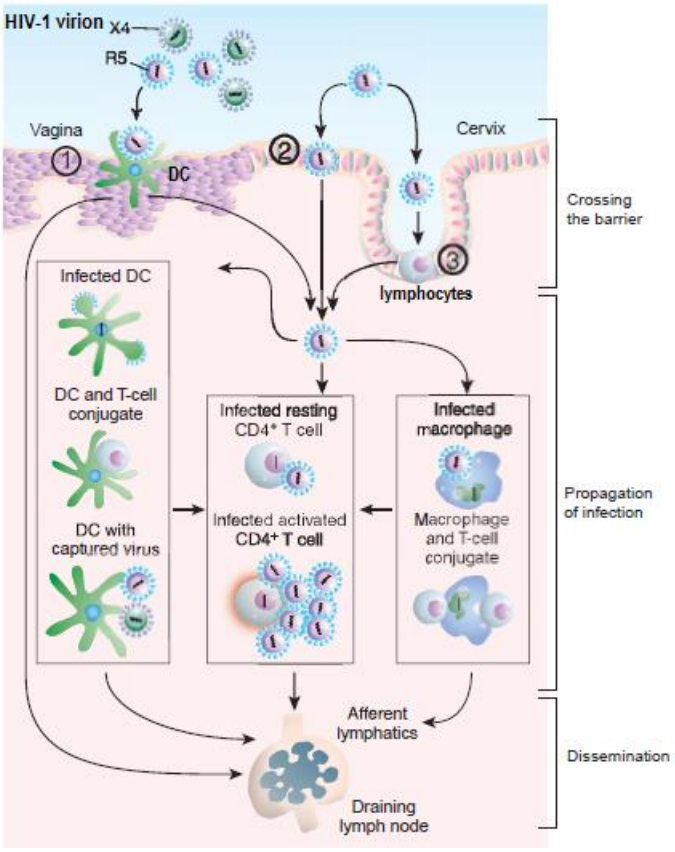


Figure 2.10. HIV-1 crossing the mucosal barrier, propagation and dissemination of infection. Adapted from Pope et al. [189]. The virus crosses the mucosal barrier by infection of dendritic cells (1), transcytosis (2), or infection of intraepithelial lymphocytes (3). Abbreviations: DC, dendritic cell; HIV, human immunodeficiency virus; R5 and X4, the CCR5 and CXCR4 viral strains, respectively.

Acute or primary infection

This stage is characterised by massive viral replication leading to high levels of viraemia (>10^7 copies of viral RNA per mL plasma), rapid virus dissemination to various lymphoid organs, the establishment of persistent viral reservoirs and depletion of CD4+ T-cells (Figure 2.11). These conditions are often associated with "flu-like" symptoms: fever, generalised lymphadenopathy, non-specific rash, myalgia and/or malaise. During this stage, both viraemia and transmissibility peak (Figure 2.11). Once the immune responses (CD8+ T-cells and HIV antibodies) develop, viraemia decreases by approximately 100-fold, accompanied by a brief

recovery of CD4+ T-cells but not to pre-infection levels [188,190-195] (Figure 2.11). Despite the production of immune responses, escape viral mutants (i.e. viral diversity) increase throughout the disease [188,194] (Figure 2.11).

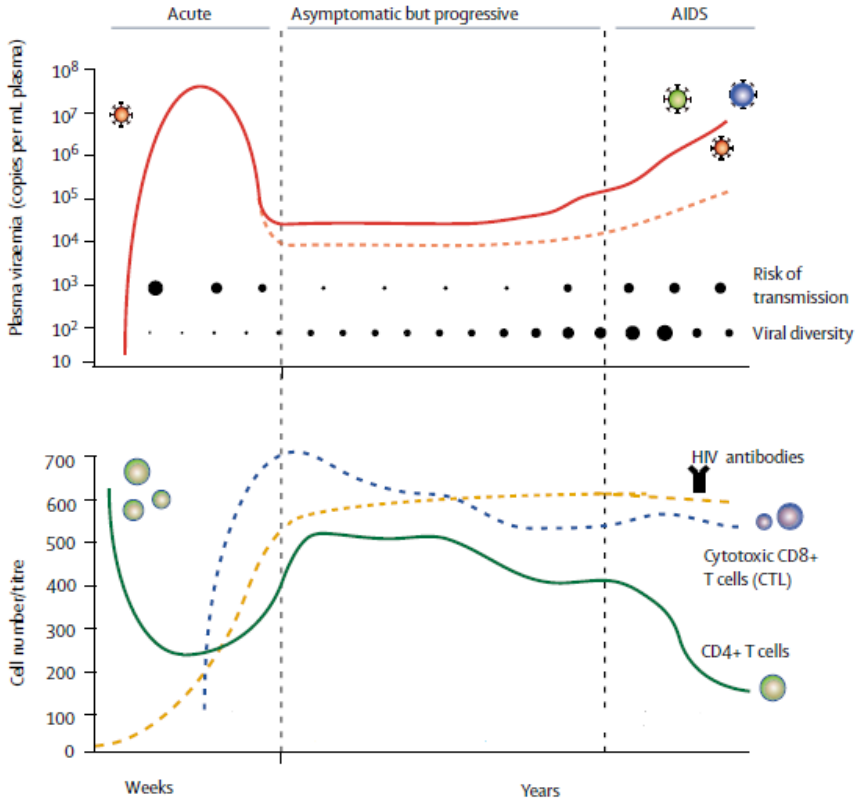


Figure 2.11. Natural history and immunopathogenesis of HIV-1 infection. Adapted from Simon et al. [194]. The progression of HIV-1 infection can be depicted as three stages: acute infection, asymptomatic and AIDS (see text). Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Chronic infection or asymptomatic

This stage begins with the establishment of viral set point – a steady-state level of viraemia (Figure 2.11). The level of viral set point varies among patients and is an important determinant of disease progression: patients with higher levels of viral set point generally progress more rapidly to AIDS and death than those with lower levels [188,191,193-195]. The chronic stage of infection is characterised by a slow and continuous increase in viraemia, progressive decrease in CD4+ T-cells and asymptomatic state [188,190-195].

AIDS

AIDS is the last disease stage characterised by a decline in CD4+ T-cells to <200 cells/μL leading to an increased risk of opportunistic infections. Control of HIV-1 infection is lost and the level of viraemia increases (Figure 2.11). Without any treatment, this stage is lethal [188,190,191,193,194].

2.5.5 Global HIV epidemic in women of reproductive age

2.5.5.1 Epidemiology

In 2019, of the estimated 38 million HIV-positive people globally, approximately 50% (19.2 million) were women aged ≥15, of whom, 11% (2.1 million) were aged 15-24 [1]. The number of new HIV infections among women and girls has steadily decreased (Figure 2.12). In 1995, approximately 1.2 million women aged ≥15 acquired HIV globally, of whom nearly 50% were 15-24 years old [196] (Figure 2.12). By 2019, that number had dropped to 720,000 with women aged 15-24 accounting for 39% (280,000) (Figure 2.12) [1]. However, this falls short of the 2020 global target of reducing the annual number of newly HIV infected young women (15-24 years) to <100,000 [197] (Figure 2.12). The trends in new HIV infections among women aged ≥15 differ across regions. Asia and the Pacific, Caribbean, sub-Saharan Africa, and Western and Central Europe and North America showed a decreasing trend between 1995 and 2018; however, Eastern Europe and Central Asia, and Middle East and North Africa showed an increasing trend [1,196]. Women and girls in sub-Saharan Africa are the most largely impacted (Figure 2.13): in 2019, they accounted for approximately 71% of the global new HIV infections [1].

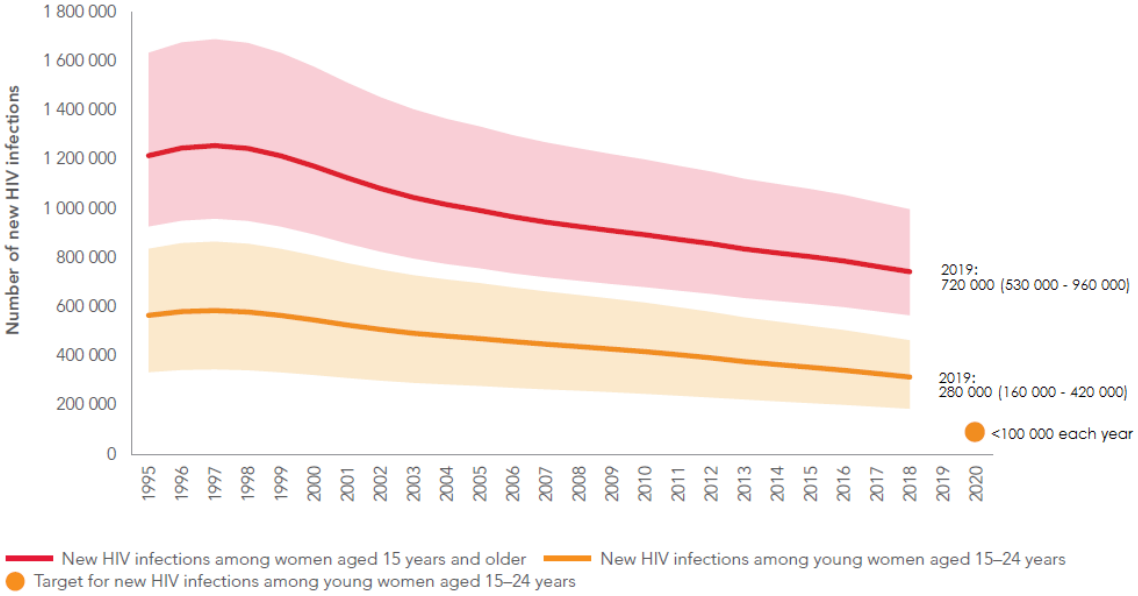


Figure 2.12. Global new HIV infections among women by age, 1995-2019 and 2020 target. Adapted from UNAIDS 2020 [196]. Abbreviations: AIDS; acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

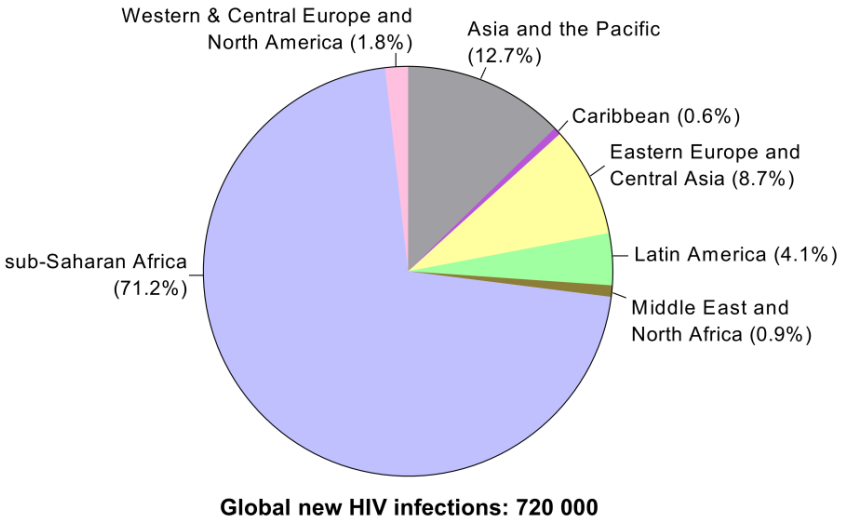


Figure 2.13. Percentage distribution of new HIV infections among women aged ≥15 by region, 2019. Data source: UNAIDS 2020 [1]. Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

Gender inequities in the context of violence, reproductive health, educational and economic opportunities and insecurity limit access to health services and, in turn, drive the HIV epidemic among women and girls, particularly those living in sub-Saharan Africa [196]. In this region, women contributed to approximately 60% of new HIV infections among adults aged ≥15 in 2019; among young people aged 15-24, women accounted for 72% of new infections [1] (Figure 2.14). Outside sub-Saharan Africa, most at-risk women or those with HIV belong to key populations: sex workers, IDUs, transgender women and prisoners. Those women face gender inequity, stigma, violence and criminalisation limiting their access to basic health services and, in turn, increase their risk of acquiring HIV. Women from key populations are 5-19 times more likely to acquire HIV than other women aged 15-49 [196].

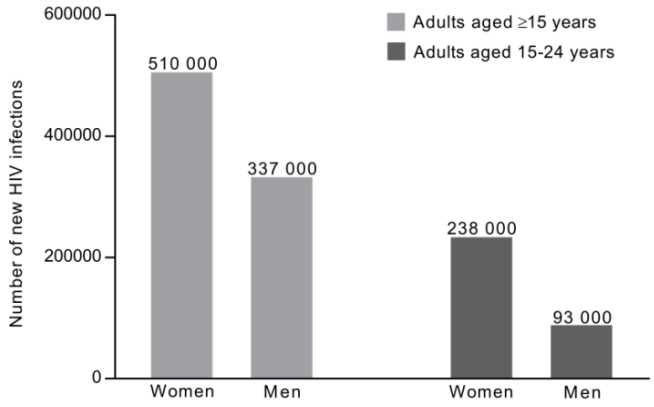


Figure 2.14. New HIV infections among women versus men by age in sub-Saharan Africa, 2019. Data source: UNAIDS 2020 [1]. Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

2.5.5.2 AIDS-related deaths in women of reproductive age

In 2019, an estimated 690,000 people worldwide died of AIDS, of whom 36.2% were women aged ≥15 [11]. Remarkable progress has been made in reducing the

number of AIDS-related deaths among those women, particularly between 2004 and 2019: from 720,000 to 250,000 deaths – a 65% reduction (Figure 2.15). In 2019, sub-Saharan Africa accounted for nearly 69% of the global AIDS-related deaths among women aged ≥15 [11] (Figure 2.15).

The rapid global scale-up of ART coverage almost certainly contributed to the decreased number of AIDS-related deaths between 2004 and 2019 (Figure 2.15). A decade ago, only 26% of women aged ≥15 received ART globally; by 2019, this proportion increased to 73%, and 65% of those on ART had suppressed viral loads [196]. In addition, the proportion of HIV-positive women aware of their HIV status has been increasing; this is in part due to HIV testing programmes offered to pregnant women visiting ANC services. In 2019, 86% of HIV-positive women (aged ≥15) worldwide knew their HIV status; this proportion was 84% in sub-Saharan Africa. However, these are still below the 2020 target of 90% [196].

2.5.5.3 HIV in pregnant women and mother-to-child transmission

Approximately 1.4 million HIV-positive women worldwide become pregnant annually; 90% of those are in sub-Saharan Africa. In 2019, 85% of the global number received ART to prevent MTCT (PMTCT), and 87% did so in sub-Saharan Africa. This contributed to the prevention of 220,000 new HIV infections globally (Figure 2.16), and 199,000 infections in sub-Saharan Africa in 2019 [3]. The global number of new paediatric HIV infections in 2019 was 150,000 (Figure 2.16); sub-Saharan Africa accounted for 84% [3]. However, this is still less than the 2020 global target of reducing the annual number of newly infected children to <20,000 [198].

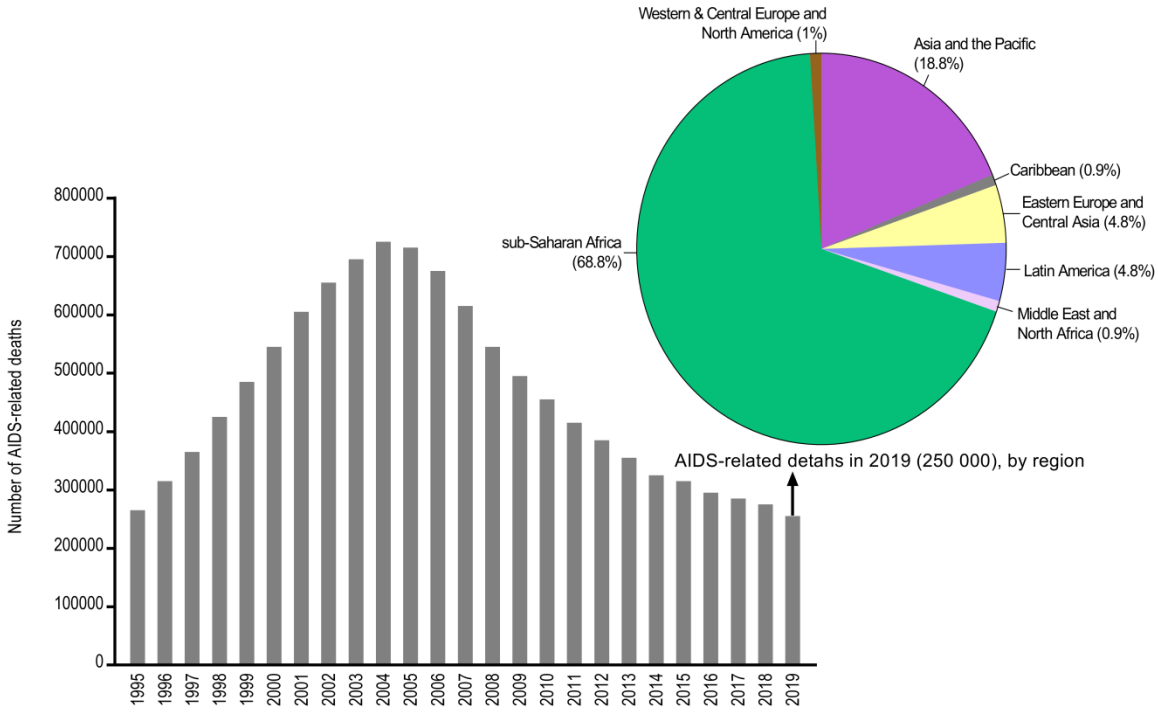


Figure 2.15. Number of AIDS-related deaths among women aged ≥15 by year and region. Data source: UNAIDS 2020 [11]. Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

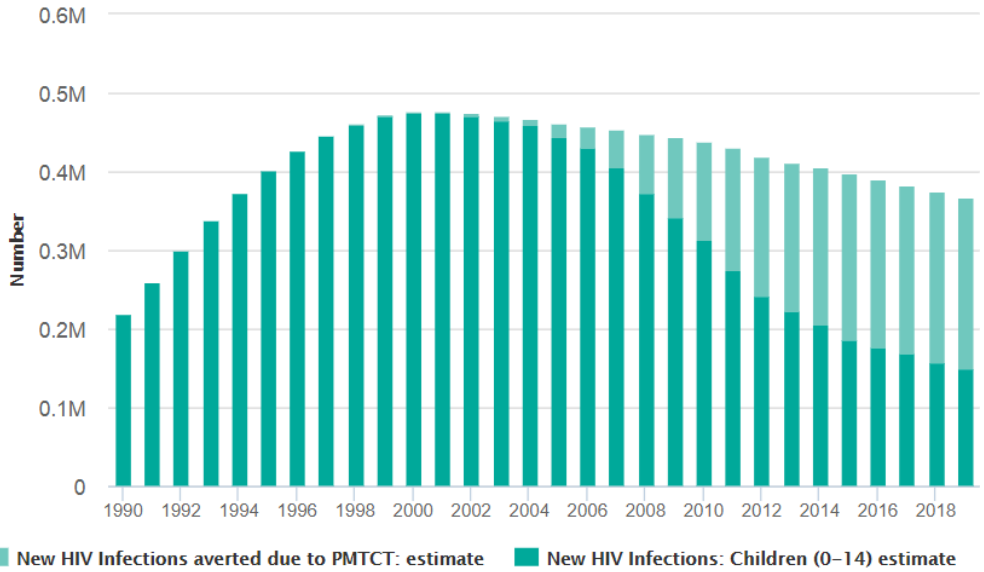


Figure 2.16. Number of new paediatric HIV infections versus number of infections averted due to PMTCT (UNAIDS 2020 [3]). Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; PMTCT, prevention of mother-to-child transmission; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

The 2019 ART coverage for PMTCT in Asia and the Pacific was 56%; the figure for the Middle East and North Africa was 30%. New HIV infections averted due to PMTCT in these two regions were 6,800 and 310, respectively [3]. Since 2015, 13 countries have been certified by WHO for the elimination of MTCT; however, none of them are in sub-Saharan Africa [199], where 84% of all newly HIV infected children reside [3].

2.6 Antiretroviral therapy

Since the introduction of HAART in the mid-1990s (Appendix 2.1: Table 2.1), HIV has changed from being a fatal infection to a manageable chronic disease. HAART has been shown to improve HIV-associated morbidity and mortality [200-202], and lower the risk of transmitting HIV to others [203-205]. The US FDA has approved five different classes of HIV medicines: 1) nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs, e.g. lamivudine); 2) non-nucleoside reverse transcriptase inhibitors (NNRTIs, e.g. efavirenz); 3) protease inhibitors (PIs, e.g. atazanavir); 4) integrase strand transfer inhibitors (INSTIs, e.g. dolutegravir); and 5) entry inhibitor, including attachment inhibitor (e.g. fostemsavir), post-attachment inhibitor (e.g. ibalizumab-uiyk), CCR5 antagonist (e.g. maraviroc) and fusion inhibitor (e.g. enfuvirtide) [206,207] (Table 2.3). The sites of action of these five classes of HIV medicines are illustrated in Figure 2.9. In addition, FDA has approved several fixed-dose combinations (FDCs) of HIV medicines (Appendix 2.3: Table 2.8). The timeline of all FDA approval for HIV medicines is provided in Appendix 2.3: Table 2.9 [206,207].

Table 2.3. HIV medicines approved by the US Food Drug and Administration.

Drug class and mechamism of action	Drug name	Trade name
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), which block the HIV reverse transcriptase enzyme by acting as host nucleotide decoys and causing termination of the elongating HIV DNA chain (Figure 2.9).	Abacavir (ABC)	Ziagen
	Didanosine (ddI)	Videx
	Emtricitabine (FTC)	Emtriva
	Lamivudine (3TC)	Epivir
	Stavudine (d4T)	Zerit
	Tenofovir disoproxil fumarate (TDF)	Viread
	Zidovudine (AZT, ZDV)	Retrovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs), which bind directly to the HIV reverse transcriptase enzyme and inhibit the function of the enzyme (Figure 2.9).	Delavirdine (DLV)	Rescriptor
	Doravirine (DOR)	Pifeltro
	Efavirenz (EFV)	Sustiva
	Etravirine (ETR)	Intelence
	Nevirapine (NVP)	Viramune
	Rilpivirine (RPV)	Edurant
Protease inhibitors (PIs), which bind to the active site of the HIV protease enzyme and inhibit the enzyme activity (Figure 2.9).	Atazanavir (ATV)	Reyataz
	Amprenavir (APV)	Agenerase
	Darunavir (DRV)	Prezista
	Fosamprenavir (FPV)	Lexiva
	Indinavir (IDV)	Crixivan
	Nelfinavir (NFV)	Viracept
	Ritonavir (RTV)	Norvir
	Saquinavir (SQV)	Invirase
	Tipranavir (TPV)	Aptivus
Integrase strand transfer inhibitors (INSTIs), which block the HIV integrase enzyme (Figure 2.9).	Dolutegravir (DTG)	Tivicay
	Elvitegravir (EVG)	Vitekta
	Raltegravir (RAL)	Isentress
Attachment inhibitor, which binds to the HIV gp120, thus preventing the virus from binding to and entering the host CD4 cells (Figure 2.9).	Fostemsavir (FTR)	Rukobia
Post-attachment inihibitor, which binds to the host CD4 receptor, thus preventing HIV from binding to the CCR5 and CXCR4 coreceptors and entering the host CD4 cells (Figure 2.9).	Ibalizumab-uiyk (TNX-355)	Trogarzo
CCR5 antagonist, which blocks viral binding (via gp120) to CCR5 coreceptor (Figure 2.9).	Maraviroc (MVC)	Selzentry
Fusion inhibitor, which blocks the fusion between the HIV envelope (via gp41) and the host CD4 cell membrane (Figure 2.9).	Enfuvirtide (T-20)	Fuzeon
Abbreviations: DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus.		

2.6.1 Antiretroviral therapy in pregnancy

The AIDS Clinical Trials Group (ACTG) protocol 076 is the first study that showed: 1) ZDV reduced the risk of MTCT by 67% and 2) was safe for both mothers and newborns [112]. Since then, many studies have been conducted in order to optimise the efficacy and safety of ART regimens so as to prevent MTCT and improve maternal health [62,63,208-220]. Following the ACTG study, in 1998, WHO published recommendations on the use of short-course ZDV for PMTCT [221]. Afterwards, WHO recommendations for ART use in pregnancy were updated several times (Table 2.4). In 2016, the "treat all" recommendation was released: an immediate initiation of lifelong EFV-based ART irrespective of clinical and immunological conditions [12]. In 2019, a recommendation for ART transition from EFV-based to DTG-based ART was published. DTG has several advantages over EFV: higher and more rapid viral suppression, and lower risk of treatment discontinuation, drug resistance and drug-drug interactions [222]. In addition, the Botswana study showed that the risk of adverse perinatal outcomes was comparable between HIV-positive pregnant women on EFV-based and DTG-based ART [97].

Table 2.4. Timeline of WHO recommendations on ART use in pregnancy.

Year	ART regimen	Eligibility criteria
1998 [221]	For PMTCT: Antepartum: ZDV from 36 weeks' gestation until labour. Intrapartum: ZDV every 3h from the onset of labour until delivery.	–Haemoglobin >8g/L.
2002 [223]	For maternal health: ZDV+3TC+NVP after the first trimester.	–WHO stage IV disease irrespective of CD4 cell count, –WHO stage I, II, or III disease with CD4 counts <200 cells/mm^3, or –WHO stage II or III disease with a total lymphocyte count <1200 cells/mm^3.

Table 2.4. Timeline of WHO recommendations on ART use in pregnancy (*continued from previous page*).

Year	ART regimen	Eligibility criteria
2003 [224]	For maternal health: d4T or ZDV+3TC+NVP after the first trimester.	–WHO stage IV disease irrespective of CD4 cell count, –WHO stage III disease with CD4 counts <350 cells/mm^3, or –WHO stage I or II disease with CD4 counts ≤200 cells/mm^3, or –WHO stage II disease with a total lymphocyte count ≤1200 cells/mm^3.
2004 [56]	For PMTCT: ZDV starting at 28 weeks' gestation and continue during labour, plus single-dose NVP at the onset of labour.	
2006 [57]	For maternal health: ZDV+3TC+NVP started as soon as practicable even if she is in the first trimester of pregnancy.	–WHO stage IV disease irrespective of CD4 cell count, –WHO stage III disease with CD4 counts <350 cells/mm^3 if available; if CD4 cell count is not available, all women in stage III should be treated, or –WHO stage I or II disease with CD4 counts <200 cells/mm^3.
	For PMTCT: Antepartum: ZDV starting at 28 weeks' gestation. Intrapartum: single-dose NVP plus ZDV+3TC. Post-partum: ZDV+3TC for seven days.	
2010 [58]	For maternal health: ZDV+3TC+NVP started as soon as eligibility is established, irrespective of gestational age, and continued throughout pregnancy, delivery, breastfeeding and thereafter.	–WHO stage III or IV disease irrespective of CD4 cell count, or –CD4 counts ≤350 cells/mm^3 irrespective of WHO clinical staging.
	For PMTCT: Option A Antepartum: ZDV starting at 14 weeks' gestation. Intrapartum: single-dose NVP plus ZDV+3TC. Post-partum: ZDV+3TC for seven days. Option B ZDV+3TC+LPV/r from as early as 14 weeks' gestation until one week after all exposure to breast milk has ended.	
2013 [59]	TDF+3TC (or FTC)+EFV initiated as soon as diagnosed with two options: Option B+: lifelong ART for all pregnant and breastfeeding women irrespective of WHO clinical stage and CD4 count. Option B: lifelong ART only for pregnant and breastfeeding women eligible for treatment (see Eligibility criteria); for those who are not eligible, ART should be stopped after delivery and cessation of breastfeeding.	For lifelong ART in option B: –WHO stage III or IV disease irrespective of CD4 cell count, or –WHO stage I or II disease with CD4 counts ≤500 cells/mm^3 (CD4 ≤350 cells/mm^3 as a priority).
2016 [12]	The "treat all" recommendation: ART should be initiated in all HIV-positive pregnant and breastfeeding women, irrespective of WHO clinical stage and CD4 cell count, and continued lifelong. ART regimen: TDF+3TC (or FTC)+EFV.	
2019 [222]	An updated first-line ART regimen: TDF+3TC+DTG.	

Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; NVP, nevirapine: PMTCT, prevention of mother-to-child transmission; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; ZDV, zidovudine.

2.7 Adverse perinatal outcomes

2.7.1 Perinatal outcomes according to gestational age at delivery

2.7.1.1 Definition

WHO defines PTB as a live birth <37 completed weeks of gestation [225]. PTB is traditionally classified by gestational age: extremely (<28 weeks), very (28 to <32 weeks) and moderate-to-late PTB (32 to <37 weeks), as well as by clinical presentation: spontaneous preterm labour, preterm prelabour rupture of membranes (PPROM) and indicated PTB [225,226]. However, PTB is a complex syndrome with multiple causes and phenotypic characteristics, i.e. it is not one disease with a single treatment. This apparent disregard for the complexity and syndromic nature of PTB, in part, has limited our understanding of PTB and its targeted preventive interventions [226-228].

The causes of most PTBs are rarely known; therefore, the optimal classification system should be based on clinical phenotype, defined as ≥1 characteristics of the mother, fetus, placenta, signs of parturition and pathway to delivery. Villar et al. [228] have identified five components that should exist in the phenotypic classification of PTB: 1) maternal conditions before presentation for delivery; 2) fetal conditions before presentation for delivery; 3) placental pathologies; 4) signs of initiation of parturition, and 5) pathway to delivery (Table 2.5). These conditions should present in the index pregnancy; therefore, PTB risk factors are not included in this phenotypic classification. Given that PTB could be the product of overlapping factors, it is possible to find >1 phenotype in a single PTB case. The phenotypic classification should improve the understanding of PTB

causes, the identification of specific at-risk groups of women and, in turn, encourage more targeted preventive interventions [226-228].

Table 2.5. Phenotypic components of the PTB syndrome proposed by Villar et al. [228].

Phenotypes	Definition
Maternal conditions	
Extrauterine infection	Significant maternal infective illness that is associated with pyrexia and the corresponding clinical manifestations (e.g. bacteremia, malaria and pyelonephritis).
Clinical chorioamnionitis	Clinically suspected intrauterine infection, manifest by maternal fever and rupture of the membranes, plus two features from maternal tachycardia, uterine tenderness, purulent amniotic fluid, fetal tachycardia and maternal leukocytosis.
Maternal trauma	A serious or critical bodily injury, wound, or shock (in turn defined as a failure of the circulatory system to maintain adequate blood flow).
Worsening maternal disease	Examples include worsening maternal cardiac, respiratory, or renal disease or hemodynamic instability that poses immediate, significant, or life-threatening risk to the mother/fetus.
Uterine rupture	A defect that occurs in the uterus and that involves the entire uterine wall; this is symptomatic and requires surgical intervention.
Preeclampsia	Gestational hypertension with proteinuria of ≥300 mg in a 24-hour period or 2 readings of at least "++" on dipstick analysis of midstream or catheter uterine specimens, if no 24-hour collection is available.
Eclampsia	Convulsions (seizures) that occur in the presence of preeclampsia and have no other cause.
Fetal conditions	
Fetal death	Intrauterine fetal death before the onset of labour (we recognise that, in some cases, it will be difficult to distinguish between recent antepartum and intrapartum deaths; however, in the consideration of the aetiologic differences, efforts must be made to establish the timing of the death).
Intrauterine growth restriction	Growth restriction (estimated fetal weight $<10^{th}$ percentile) with abnormal umbilical artery blood flow, abnormal fetal heart rate, or abnormal biophysical profile.
Abnormal fetal heart rate/ biophysical profile	Abnormal fetal heart rate: antepartum persistently reduced short-term variability or decelerations. Abnormal biophysical profile: biophysical profile of ≤6/10.
Infection/fetal inflammatory response syndrome	Infection: usually the presence of clinical chorioamnionitis with fetal tachycardia or neonatal sepsis. Fetal inflammatory response syndrome: systemic fetal inflammation and elevated fetal plasma interleukin-6 levels.
Invasive intrauterine procedures	Invasive procedures that include prenatal diagnosis (e.g. amniocentesis, chorionic villus sampling), fetal blood sampling, and endoscopic procedures (e.g. laser ablation of placental vessels, fetoscopy).
Multiple fetuses	Multiple pregnancy, subdivided into the number of fetuses and by chorionicity: 1) twin-twin transfusion syndrome, at any stage that is diagnosed on ultrasound scanning; 2) death of a fetus in multiple pregnancy, intrauterine death of ≥1 of the fetuses with live co-multiple fetuses that is confirmed by ultrasound scanning.
Fetal anomaly	Fetal structural abnormality by ultrasound scanning or during neonatal examination.

Table 2.5. Phenotypic components of the PTB syndrome proposed by Villar et al. [228] (*continued from previous page*).

Phenotypes	Definition
Fetal conditions	
Fetal anaemia	Fetal anaemia that is caused by immune factors that are suggested by: 1) haematocrit or haemoglobin concentration >2 SD below the mean for gestational age, or 2) middle cerebral artery Doppler peak systolic velocity of >1.5 multiples of the media.
Polyhydramnios	Excess amniotic fluid subjectively or objectively that is measured as amniotic fluid index above the 95th percentile for gestational age or a maximum vertical pool of at least 8 cm.
Oligohydramnios	Reduced amniotic fluid subjectively or objectively measured as amniotic fluid index below the 5th percentile for gestational age or a maximum vertical pool of 2 cm.
Placental pathologies	
Histologic chorioamnionitis	The presence of inflammatory infiltrate of neutrophils in the chorionic plate and extraplacental membranes, histologic evidence of vasculitis/ infarction/necrosis, or other histologic/microscopic findings (e.g. villitis, thrombosis).
Placental abruption	Premature separation of the placenta from the uterine wall that is diagnosed by a combination of vaginal bleeding, maternal abdominal pain and retroplacental blood clot at delivery.
Placenta praevia	Implantation of the placenta over the internal os of the cervix.
Fetal-maternal haemorrhage	Evidence of fetal-maternal haemorrhage on the Kleihauer test.
Other placental abnormalities	Placental abnormalities that may lead to or necessitate delivery (e.g. placental giant chorioangioma, circumvallate placenta).
Signs of initiation of parturition	
Cervical shortening	Shortening of the uterine cervix on clinical and/or ultrasound examination.
Preterm prelabour rupture of the membranes	Rupture of the amniotic membranes before the onset of labour at <39 weeks' gestation.
Regular contractions	Regular uterine contractions that lead to cervical effacement or dilatation.
Cervical dilatation	Dilatation of the uterine cervix on clinical examination.
Bleeding	Any evidence of bleeding from the uterus or cervix.
Unknown initiation	Cases in which it is not possible to establish the initial step in the parturition process.
Pathway to delivery – caregiver initiated	
Clinically mandated	Cases in which the caregiver initiates delivery because there is an immediate and significant or life-threatening risk to the mother/fetus (e.g. for severe preeclampsia).
Clinically discretionary	Cases in which the caregiver initiates delivery although there is no immediate or significant risk to the mother/fetus but in which there may be some evidence that delivery may be associated with a better outcome.
No clinical indication	Cases in which the caregiver initiates delivery for reasons (such as errors in gestational age estimation, convenience of timing, precious fetus, maternal request) that were stated on or inferred from the medical records.
Pregnancy termination	Cases in which termination is caused for reasons such as fetal abnormality, medical contraindication to pregnancy, or maternal request.
Unknown reason	Cases in which the caregiver initiates delivery, but there is no documentation of any indication or supporting information of any indication, including a range of several less-well understood social and personal factors that are seldom documented that could motivate preterm birth.

Table 2.5. Phenotypic components of the PTB syndrome proposed by Villar et al. [228] (*continued from previous page*).

Phenotypes	Definition
Pathway to delivery – spontaneous	
Regular contractions	Regular uterine contractions that lead to cervical effacement or dilatation.
Augmented	Augmentation or stimulation of uterine contractions by oxytocin without spontaneous contractions.

Villar et al. [229] conducted a population-based, multinational study including a total of 5,828 PTBs ($\geq 16^{+0}$, $<37^{+0}$ weeks' gestation) in order to assign PTB phenotypes using their new classification system. They identified 12 PTB phenotypic clusters: the largest cluster (30% of the total PTBs) was not associated with any maternal, fetal, or placental conditions; 11 clusters comprised of combinations of conditions related to PTB (Table 2.6). Of these 11 clusters, 10 were dominated by a single condition and only one was not (Table 2.6). Clusters 5, 8, 9, 11 and 12 showed the highest neonatal mortality and morbidity rates (Table 2.6). Other studies [230-232] employing the phenotypic classification of Villar et al. [228] are presented in Table 2.7.

Esplin et al. [233] developed a different phenotypic classification tool, which includes nine clinical phenotypes: infection/inflammation, decidual haemorrhage, maternal stress, cervical insufficiency, uterine distention, placental dysfunction, PPROM, maternal comorbidities and familial. Each phenotype has three levels of evidence: strong, moderate and possible (Appendix 2.4: Table 2.10). Based on this phenotypic tool, they identified five clusters of spontaneous PTB (≤34 weeks' gestation): cluster 1, which was dominated by maternal stress; cluster 2 PPROM; cluster 3 familial factors; cluster 4 maternal comorbidities; and cluster 5 multifactorial (infection, decidual haemorrhage and placental dysfunction) [233].

Table 2.6. Distribution of the 12 clusters of PTB phenotypes according to maternal, fetal and placental conditions, and NICU admission and neonatal mortality rates (Villar et al. [229]).

Cluster	N (%)	Main condition (%)	Most frequent associated conditions (%)	NICU ≥7 days, %	NMR/1000[§]
1	1,747 (30.0)	None	None	13.9	5
2	689 (11.8)	Preeclampsia (100)	Third-trimester bleeding and preeclampsia (72.6), extrauterine infection (28.6) and suspected IUGR (24.4)	45.8	36
3	607 (10.4)	Multiple births (100)	Extrauterine infection (21.9) and suspected IUGR (21.3)	31.2	24
4	450 (7.7)	Extrauterine infection (100)	Mid-pregnancy bleeding (20.4), chorioamnionitis (12.7) and severe maternal conditions (12.7)	26.3	36
5	443 (7.6)	Chorioamnionitis (100)	Multiple births (25.1), perinatal sepsis (14.7) and suspected IUGR (9.7)	37.7	43
6	362 (6.2)	Mid-/late-pregnancy bleeding (100)	Chorioamnionitis (21.8), perinatal sepsis (16.0) and multiple births (14.9)	38.9	27
7	337 (5.8)	Suspected IUGR (100)	Fetal distress (18.4), severe maternal conditions (18.4) and mid-/late-pregnancy bleeding (7.7)	42.4	28
8	319 (5.5)	Perinatal sepsis (68.0)	Congenital anomalies (41.4), multiple births (30.1) and fetal anaemia (23.8)	66.8	99
9	280 (4.8)	Early bleeding (100)	Multiple births (27.9), extrauterine infection (25.0) and mid-/late-pregnancy bleeding (22.5)	31.8	68
10	213 (3.7)	Antepartum stillbirth (100)	Severe maternal conditions (23.9), extrauterine infection (13.6) and mid-/late-pregnancy bleeding (13.1)	NA	NA
11	200 (3.4)	Fetal distress (100)	Severe maternal conditions (7.5), congenital anomalies (6.5) and chorioamnionitis (4.5)	26.6	45
12	181 (3.1)	Severe maternal conditions (100)	Multiple births (28.7), chorioamnionitis (24.3) and congenital anomalies (8.3)	22.4	37
All cases	5,828 (100)			29.5	30

[§]Death during hospital stay.
Abbreviations: IUGR, intrauterine growth restriction; NA, not applicable; NICU, neonatal intensive care unit; NMR, neonatal mortality rate; PTB, preterm birth.

Table 2.7. Studies employing the PTB phenotypic classification system proposed by Villar et al. [228].

Author	Country	No of PTBs	Findings
Souza et al. 2019 [230]	Brazil	4,150 PTBs	The study identified three clusters of PTB phenotypes: 1) women without any predefined conditions; 2) women with mixed conditions (e.g. extrauterine infection, chronic disease, mid-/late-pregnancy bleeding); and 3) women with preeclampsia, eclampsia, HELLP syndrome and fetal growth restriction.
Maghsoudlou et al. 2019 [231]	Canada	6,983 PTBs of nulliparous women	Two thirds of nulliparous women had ≥1 clinical phenotypes and the remaining one third did not have any predefined phenotypes. The most common phenotypes: worsening of maternal disease, IUGR and fetal distress.
Maghsoudlou et al. 2019 [232]	Canada	8,775 PTBs of multiparous women	At least one clinical phenotype was observed in 66% of multiparous women with a history of PTB and 63% of those without a history of PTB. The most common phenotypes in these two groups of multiparous women: worsening maternal disease, IUGR, fetal distress and extrauterine infection.

Abbreviations: HELLP, haemolysis, elevated liver enzymes, low platelet; IUGR, intrauterine growth restriction; PTB, preterm birth.

2.7.1.2 Epidemiology

The true prevalence of PTB is unknown. This is mainly due to the scarcity of accurate data, particularly from LMICs [6,234,235]. In a recent study investigating global PTB rates [6], only 38 of 107 countries (36%) had adequate data, enabling a direct report of PTB rates; the remaining 69 (64%) had poor-quality data, requiring a modelling analysis. Using the 2010 data of 184 countries, an estimated 15 million PTBs occur annually, corresponding to the global rate of 11%: ranging from 4% in Belarus to 18% in Malawi [234]. Of the 15 million annual PTBs, more than 84% are moderate-to-late PTB, 10% very PTB, and only 5% extremely PTB. India, China, Nigeria, Pakistan, Indonesia and the USA contributed to approximately 50% (7.4 million) [235]. The most recent estimates showed that PTB rates increased in most countries; the global PTB rate increased from 9.8% in 2000 to 10.6% in 2014 [6].

There are disparities in PTB rates by country-income status [235], region [6], ethnicity [236] and education [237]. According to the World Bank income classification, LMICs accounted for 90% of the global PTBs; the average PTB rates in low, middle and high-income countries are 12%, 9.4% and 9.3%, respectively. However, outliers may exist; for instance, the PTB rate in Ecuador (5%, middle-income country) is lower than that in several high-income countries: Canada (7.8%) and Germany (9.2%) [235]. By region, the 2014 data showed that 81% of the global PTBs were in Asia and sub-Saharan Africa. However, within-region differences were observed: for example, the PTB rate in Uganda was 6.6% compared to 16.6% in Tanzania [6]. By maternal ethnicity, US African-American women (14%) had a higher PTB rate than white women (9%) in 2016 [236]. By maternal education, a meta-analysis of 12 European countries showed that women with lower education levels had a higher PTB rate than those with higher education levels; this was most marked in the Netherlands (7.0% versus 4.9%) and Norway (9.7% versus 5.9%) [237].

2.7.1.3 Complications

PTB is the leading cause of under-5 mortality, contributing to 18% of under-5 and 35% of neonatal deaths [73]. The majority of these deaths occur in the first week of life because of increased susceptibility to infections [238-240], particularly in LMICs, where basic interventions (e.g. antenatal corticosteroids, Kangaroo mother care and treatment of neonatal infections) and neonatal intensive care services are lacking or very expensive [235,238,241,242]. This might have led to the 90:10 survival gap, i.e. more than 90% of babies born <28 weeks' gestation

survive in high-income countries; however, only 10% of these babies survive in low-income countries [235].

A pooled analysis in LMICs showed that the relative risks of neonatal mortality increased with decreasing gestational age: very PTB (<32 weeks' gestation) exhibited the highest risk compared to moderate (32 to <34 weeks) and late PTB (34 to <37 weeks) [238] (Figure 2.17). Remarkable advancements in perinatal, neonatal and paediatric care have improved the survival of PTB babies. In most developed countries, more than 95% of babies born <37 weeks' gestation, 90% of those born <28 weeks' gestation and 50% of those born <25 weeks' gestation survive beyond the neonatal period or even to adulthood [235,243,244]. However, these survivors are at an increased risk of developing long-term adverse outcomes [243,245-248] (Table 2.8).

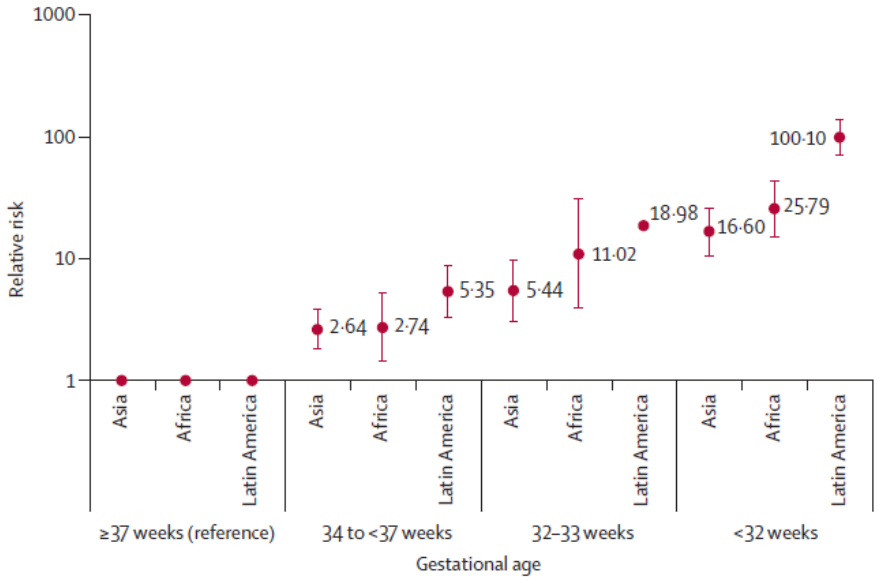


Figure 2.17. Relative risks of neonatal mortality associated with gestational age in low and middle-income countries (Katz et al. [238]).

Table 2.8. Long-term adverse outcomes in survivors of preterm birth.

	Long-term adverse outcomes
Pulmonary function abnormalities and chronic lung diseases	Reduced exercise capacity, reduced lung function, bronchopulmonary dysplasia, respiratory symptoms (e.g. exertional dyspnea), asthma and obstructive lung disease.
Sleep issues	Obstructive sleep apnea syndrome, snoring and sleep disruption (periodic limb movement).
Cardiovascular and metabolic outcomes	Higher blood pressure or hypertension, ischemic heart disease, venous thromboembolic events, type 2 diabetes mellitus, dyslipidemia, obesity and abnormal depositions of fat in organs.
Renal outcomes	Chronic kidney disease and hypertension.
Neuropsychiatric, cognitive and functional outcomes	Lower tendency for risk-taking behaviours; more likely to exhibit social withdrawal, introversion, neuroticism; depression; the triad of psychiatric conditions (anxiety, inattention and autistic traits); psychosis; schizophrenia; mood and eating disorders; impairments in brain and motor function, speech and learning; bullying, peer victimization and social exclusion; lower intelligence quotient scores, higher unemployment and lower earning capacity; more likely to remain single, have a lower rate of sexual intercourse and lower self-esteem.
Neonatal intraventricular haemorrhage or white matter injury	Poor neurologic outcomes, e.g. coordination disorder and long-term motor impairment.
Accelerated ageing	Age-related conditions (e.g. hypertension, ischemic heart disease) and reduced life span.

2.7.2 Perinatal outcomes according to birth weight

2.7.2.1 Definition

Birth weight is the first weight measured after birth. For live newborns, this measurement should be performed within the first hours of life, i.e. before post-natal weight loss. WHO defines (regardless of gestational age) LBW as a birth weight <2,500g, very LBW as <1,500g and extremely LBW as <1,000g. The LBW definition is based on epidemiological observations that babies with birth weight <2500g are 20 times more likely to die than heavier babies. It was mentioned in the 2004 WHO report that this practical cut-off is mainly used for international health statistics comparisons, and not appropriate for clinical

settings. For clinical purposes, WHO encouraged individual countries to determine alternative cut-off values [249-251].

LBW is either the result of PTB, IUGR (proxied by SGA: <10th centile of birth weight for gestational age and sex), or a combination of these two conditions [238,249,250]. Therefore, ideally, LBW should be stratified into three groups: LBW in appropriately grown preterm neonates and LBW in term and preterm growth restricted neonates (Figure 2.18). However, this stratification seems very difficult in settings with limited access to ultrasound facilities [7,238,252].

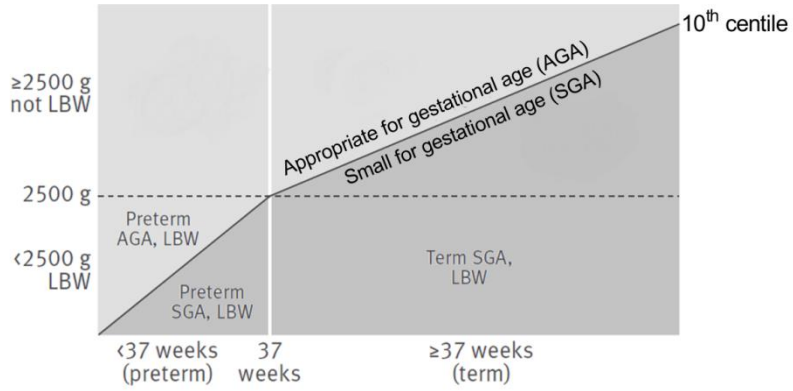


Figure 2.18. The relation between birth weight and gestational age. Adapted from Lee et al. [7]. Abbreviations: AGA, appropriate for gestational age; LBW, low birth weight; SGA, small for gestational age.

LBW has long been used as a surrogate indicator of infant mortality risk and a target of public health interventions [249-251]. WHO has targeted a 30% reduction in LBW prevalence between 2012 and 2025; an average annual reduction rate (AARR) of 2.74% is required to meet this target [250]. One reason for this is a strong association between LBW and infant mortality, as mentioned above [249,251]. Another reason is that birth weight data are more readily available (i.e. precisely recorded, free and available in vast numbers) in most

settings unlike gestational age, which needs a first-trimester ultrasound to obtain the most accurate estimate. Existing evidence also suggests that LBW is an unreliable marker of perinatal health [251,253-255].

2.7.2.2 Epidemiology

The estimated global LBW prevalence in 2015 was 14.6%; compared to the prevalence in 2000 (17.5%), there was a 16.6% reduction between these two periods (AARR: 1.23%) [256] (Figure 2.19). Despite this progress, a more than double reduction is needed to achieve the AARR target of 2.74% between 2012 and 2025 [250,256]. The absolute number of LBWs in 2015 was 20.5 million, 91% of those were from LMICs, particularly south Asia (9.8 million; 48%) and sub-Saharan Africa (5 million; 24%) [256] (Figure 2.20). In addition, of the estimated 18 million LBW babies born in LMICs in 2010, 10.6 million (59%) were term-SGA, 2.8 million (16%) preterm-SGA and 4.6 million (25%) preterm and appropriate size for gestational age [257] (Figure 2.21).

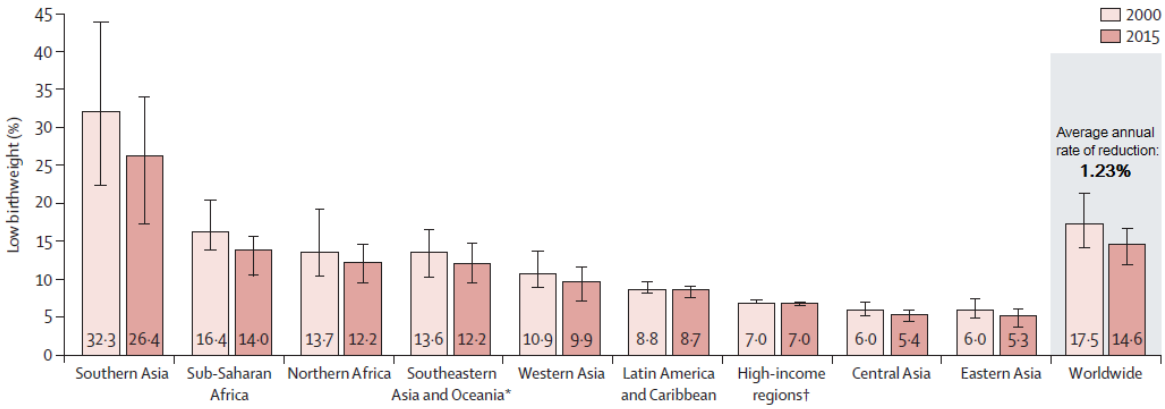


Figure 2.19. Regional and global change in low birth weight prevalence between 2000 and 2015. Adapted from Blencowe et al. [256]. *Southeastern Asia and Oceania do not include Australia or New Zealand. †High-income regions include North America, Europe and Australia and New Zealand.

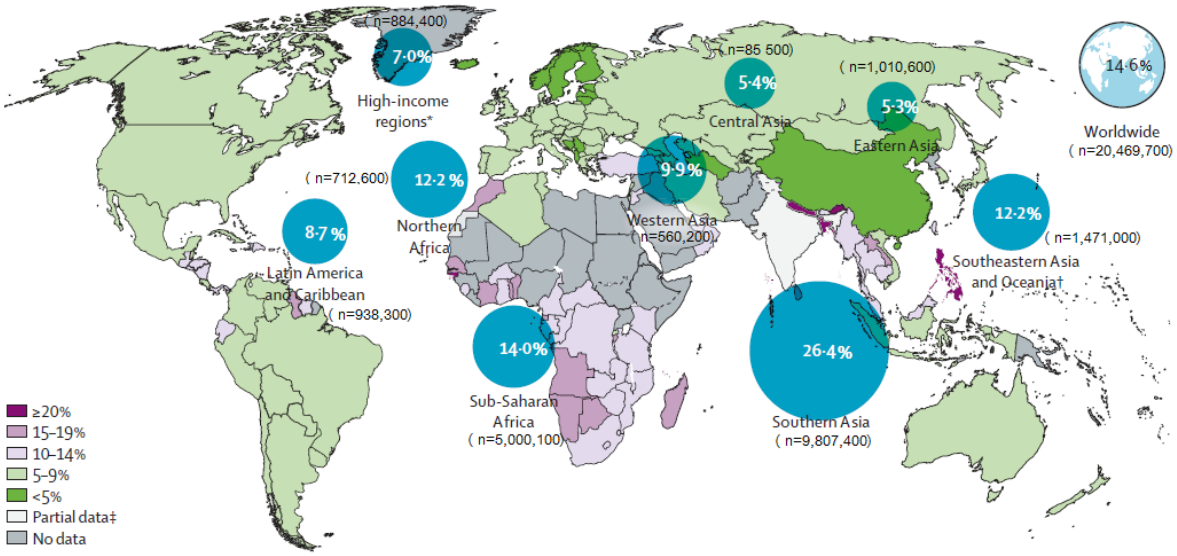


Figure 2.20. National, regional and global number and prevalence of low birth weight, 2015. Adapted from Blencowe et al. [256]. *High-income regions include North America, Europe and Australia and New Zealand. †Southeastern Asia and Oceania do not include Australia or New Zealand.

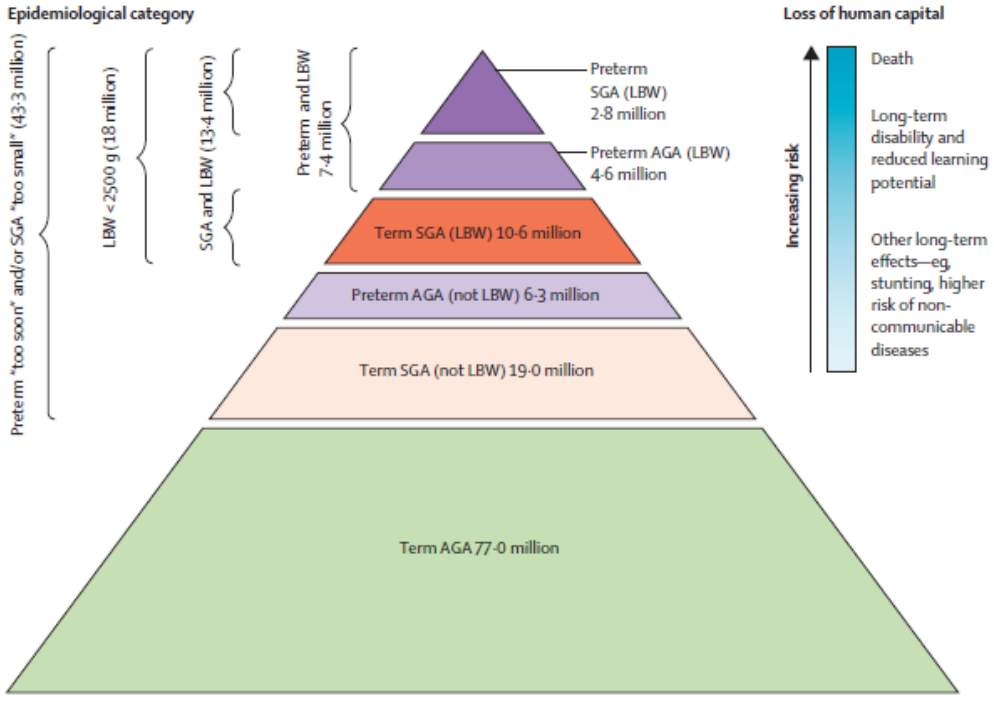


Figure 2.21. The burden of preterm birth, low birth weight and small for gestational age in low and middle-income countries, 2010 [Lee et al. [257]). Abbreviations: AGA, appropriate for gestational age; LBW, low birth weight; SGA, small for gestational age.

2.7.2.3 Complications

More than 80% of NNDs worldwide every year are LBW [74,258]. A recent study in LMICs showed that the odds ratios of NND in the first week of life increased with decreasing birth weight [259] (Figure 2.22). LBW newborns who survive are at greater risk of post-neonatal death, neonatal morbidities (birth asphyxia, acute respiratory infection and diarrhea), growth failure and long-term adverse outcomes (neurological and language development disorders, metabolic and cardiovascular diseases and poor academic performance) [74,257-259] (Figure 2.21).

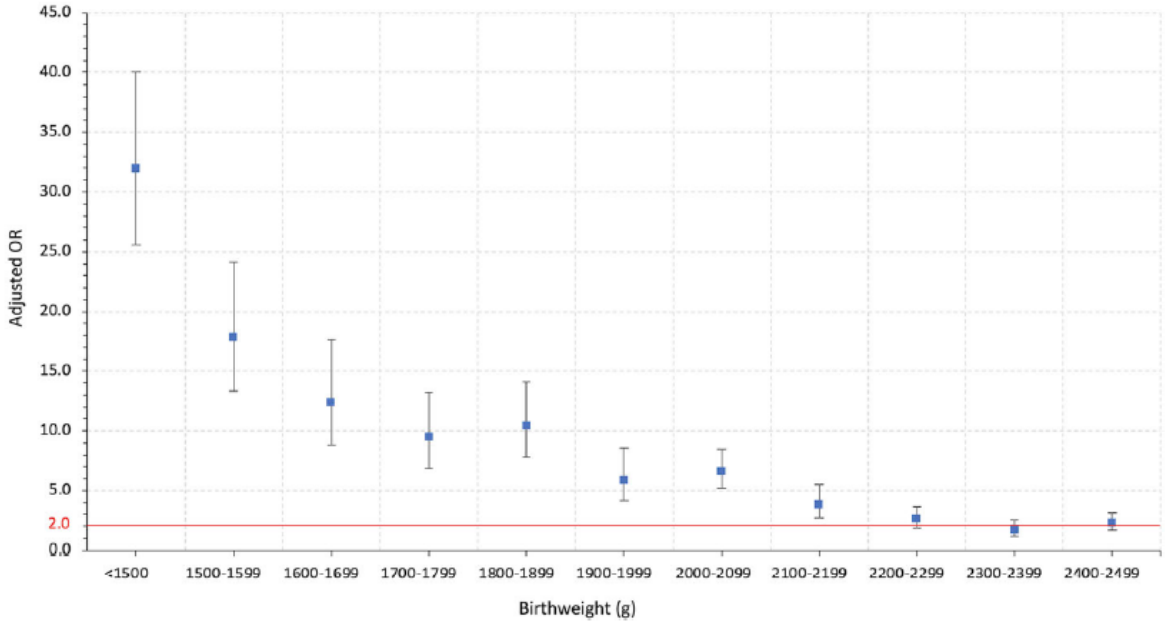


Figure 2.22. Adjusted odds ratios and 95% confidence intervals of neonatal death in the first week of life by birth weight [Laopaiboon et al. [259]]. Reference group: babies with birth weight 2,500-3,499g. Solid red line indicates the adjusted odds ratio 2.0, clinical significance criterion used by the study. Abbreviation: OR, odds ratio.

2.7.3 Perinatal outcomes according to gestational age and birth weight combined

2.7.3.1 Definition

LBW was mistakenly used to define prematurity from the 1920s to the 1960s [251,260]. However, epidemiological data show that not all LBW babies are premature, and not all premature babies are LBW. In 1961, WHO suggested that LBW should not be used to define prematurity [261]. When prematurity is redefined using gestational age, there remain a large number of LBW babies born at term with a high risk of mortality. This condition led to the recognition of a new pathology: intrauterine growth restriction (IUGR) [251,260]. In addition, babies with the same birth weight but different gestational ages develop different clinical problems. This suggests a disparity between birth weight and gestational age, either too small (i.e. small for gestational age, SGA) or too large (i.e. large for gestational age, LGA) (262). SGA is defined as a birth weight <10^{th} centile for a specific completed gestational age by sex (262), and is commonly used as a proxy for IUGR (7)(251)(260)(262). Very SGA (VSGA) is defined as a birth weight <3^{rd} centile for gestational age. LGA is defined as a birth weight >90^{th} centile for gestational age. A birth weight for gestational age between the 10^{th} and 90^{th} centile is considered as appropriate for gestational age (AGA) (262).

2.7.3.2 Epidemiology

The vast majority of SGA babies are born in LMICs (7)(257); however, the estimates of SGA vary depending on the reference population used (7)(263). For example, the estimated number of SGAs in LMICs in 2012 based on the

INTERGROWTH-21st Newborn Size Standards (23.3 million) was 27% lower than that based on the US 1991 Birth Weight Reference (31.9 million) [7] (Table 2.9). Despite this, the INTERGROWTH-21st standard (18.1 million; 78%) and the US 1991 reference (24.8 million; 78%) agreed that the majority of SGAs in 2012 occurred in south Asia and sub-Saharan Africa [7] (Table 2.9). When the SGA estimates based on the US 1991 reference in 2010 (32.4 million; 27% of live births) and 2012 (31.9 million; 26.4% of live births) are compared they were similar [7,257] (Table 2.9). Furthermore, the 2010 data estimated that 3.9 million babies (23%) were born VSGA in south Asia (257).

INTERGROWTH-21st is the first international, multinational birth weight for gestational age standard including pregnancies with accurate dating (ultrasound <14 weeks' gestation), optimal nutrition, health (i.e. no relevant morbidities) and socio-economic conditions; detailed inclusion criteria can be found in Villar et al. [264]; newborn measurements were conducted within 12h of birth using standardised procedures across sites. Their research provided a single universal standard to describe optimal newborn size for gestational age around the world, whereas the US 1991 reference included pregnancies from the general population with less accurate dating (LMP) [265].

Table 2.9. SGA births in LMICs in 2010 and 2012 comparing the INTERGROWTH-21st Newborn Size Standards to the US 1991 Birth Weight Reference.

UN-MDG regions	2010[§]			2012[ǀ]				
	Live births (1000s)	US 1991 Reference		Live births (1000s)	INTERGROWTH-21st		US 1991 Reference	
		Number of SGA (1000s)	SGA prevalence (%)		Number of SGA (1000s)	SGA prevalence (%)	Number of SGA (1000s)	SGA prevalence (%)
Caucasus and central Asia	1,643.0	240.7	15.0	1,774.3	195.5	11.0	260.7	14.7
East Asia	17,490.0	1,182.3	7.0	19,097.2	949.5	5.0	1,311.2	6.9
Southeast Asia	10,983.4	2,670.2	24.3	9,691.1	2,089.9	21.6	2,771.5	28.6
South Asia	38,753.0	17,350.3	44.5	36,625.8	12,537.7	34.2	16,304.4	44.5
West Asia	4,855.3	1,066.9	21.8	4,844.9	756.6	15.6	996.9	20.6
Oceania	263.1	55.3	21.0	266.4	42.7	16.0	55.7	20.9
North Africa	3,543.0	337.6	9.6	3,989.8	248.2	6.2	381.5	9.6
Sub-Saharan Africa	32,085.5	8,157.3	25.5	33,727.5	5,575.2	16.5	8,483.7	25.2
Latin America and the Caribbean	10,844.5	1,374.0	12.5	10,833.3	930.3	8.6	1,379.1	12.7
Total	120,461.3	32,434.8	27.0	120,850.2	23,325.6	19.3	31,944.8	26.4

[§] Source: Lee et al. [257].
[ǀ] Source: Lee et al. [7].
Abbreviations: LMICs, low and middle-income countries; SGA, small for gestational age; UN-MDG, United Nations – Millennium Development Goals.

2.7.3.3 Complications

SGA is associated with an increased risk of neonatal and post-neonatal deaths compared to AGA, with pooled relative risks of nearly 2 in LMICs. These risks increase with SGA severity, with VSGA exhibiting the highest risks (Figure 2.23). These risks are even higher among babies born both preterm and SGA than among those with PTB or SGA alone (Figure 2.24) [238].

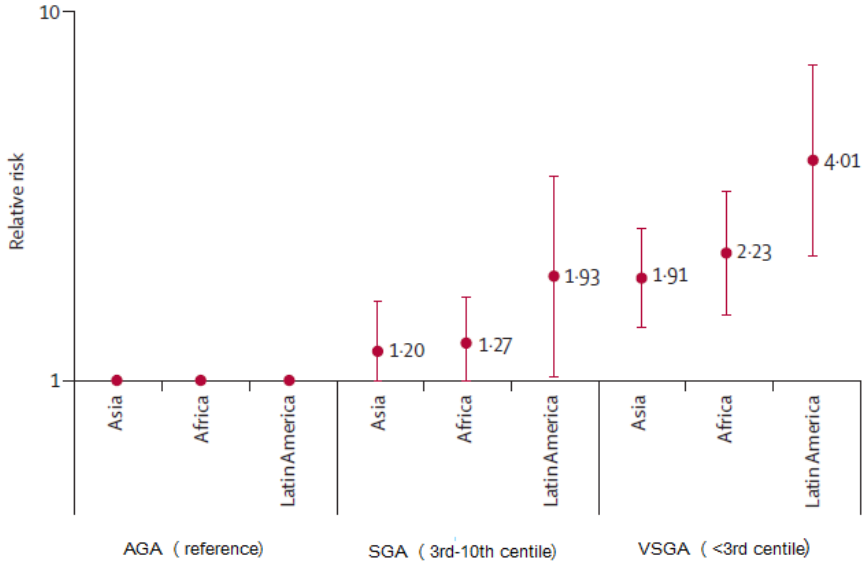


Figure 2.23. Relative risks of neonatal death associated with small for gestational age in low and middle-income countries. Adapted from Katz et al. [238]. Abbreviations: AGA, appropriate for gestational age; SGA, small for gestational age; VSGA, very small for gestational age.

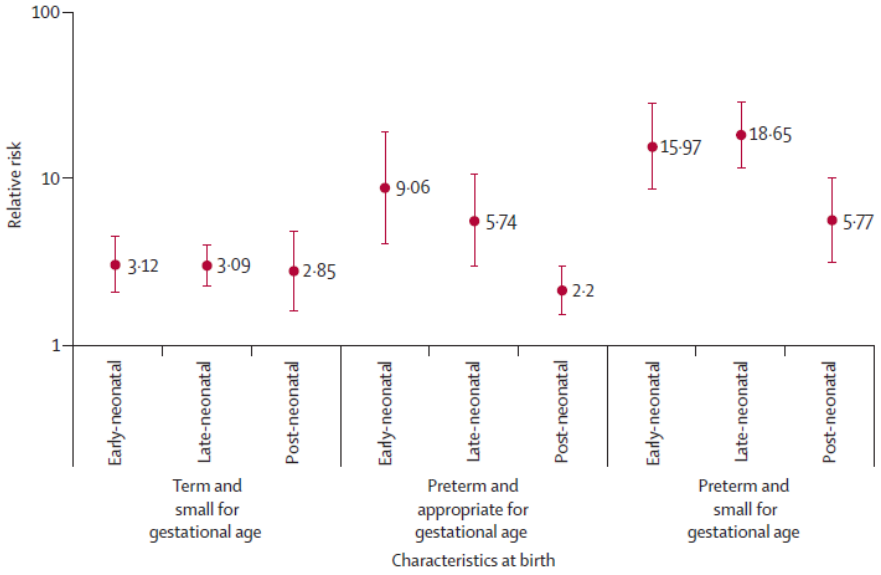


Figure 2.24. Relative risks of neonatal and post-neonatal deaths associated with preterm birth and small for gestational age in low and middle-income countries (Katz et al. [238]). Reference: babies born term and appropriate for gestational age.

In 2012, an estimated 606,500 NNDs in LMICs were attributable to SGA based on the INTERGROWTH-21st standard; this number was 27% higher when the US 1991 reference was used to define SGA [7] (Table 2.10). The highest number of NNDs attributable to SGA was in South Asia (INTERGROWTH-21st standard: 289,700; US 1991 reference: 359,300) (Table 2.10), where the prevalence of SGA was the highest (INTERGROWTH-21st standard: 34.2%; US 1991 reference: 44.5%) (Table 2.9) [7]. Furthermore, SGA is associated with a higher risk of: 1) infections, respiratory depression, jaundice, polycythaemia, hypoglycaemia, poor feeding and hypothermia in the neonatal and post-neonatal periods [266,267]; 2) delayed neurodevelopment, poor linear growth and stunting in childhood [268,269]; 3) obesity, insulin resistance, dyslipidaemia, hypertension and ischaemic heart disease in adulthood [270,271].

Table 2.10. Neonatal deaths attributable to SGA in LMICs in 2012 comparing the INTERGROWTH-21st Newborn Size Standards to the US 1991 Birth Weight Reference.

UN-MDG regions	No of NNDs	INTERGROWTH-21st		US 1991 Reference	
		No of NNDs attributable to SGA	% of NNDs attributable to SGA	No of NNDs attributable to SGA	% of NNDs attributable to SGA
Caucasus and central Asia	26,500	3,800	14.3	5,500	20.6
East Asia	158,900	16,100	10.1	25,100	15.8
Southeast Asia	143,900	33,000	22.9	45,100	31.3
South Asia	1,127,300	289,700	25.7	359,300	31.9
West Asia	63,400	11,000	17.4	14,700	23.2
Oceania	5,700	900	15.8	1,200	20.6
North Africa	50,600	5,200	10.3	7,000	13.8
Sub-Saharan Africa	1,090,200	219,300	20.1	277,100	25.4
Latin America and the Caribbean	105,900	27,300	25.8	37,100	35.0
Total	2,772,400	606,500	21.9	772,000	27.8

Source: Lee et al. [7].
Abbreviations: LMICs, low and middle-income countries; NNDs, neonatal deaths; SGA, small for gestational age; UN-MDG, United Nations – Millennium Development Goals.

2.7.4 Perinatal outcomes according to fetal and neonatal mortality

2.7.4.1 Miscarriage and stillbirth

2.7.4.1.1 Definition

Miscarriage and stillbirth are variously defined. Table 2.11 provides the definitions of miscarriage and stillbirth according to the WHO/International Classification of Diseases-10th revision (ICD-10)/United Nations Children's Fund (UNICEF) [240,272-276]; American College of Obstetricians and Gynecologists (ACOG)/Centers for Disease Control and Prevention (CDC)/National Center for Health Statistics (NCHS), US [277,278]; and Royal College of Obstetricians & Gynaecologists (RCOG), UK [279-281].

Table 2.11. Definitions of miscarriage and stillbirth.

	Definitions
Miscarriage	
WHO/ICD-10	The expulsion or extraction of a fetus or embryo weighing <500g, equivalent to approximately <22 weeks' gestation or body length (crown-heel) <25cm [272-274].
	Pregnancy loss <28 weeks' gestation [274,282].
CDC/NCHS	The expulsion or extraction of a fetus of <20 weeks' gestation or weighing <350g [277].
RCOG	The spontaneous loss of pregnancy from the time of conception until <24 weeks' gestation [279,280].
Stillbirth	
WHO/ICD-10/ UNICEF	Early fetal death: a death at a birth weight of ≥500g, a gestational age of ≥ 22 weeks, or a body length ≥25cm; late fetal death: birth weight ≥1,000g, gestational age ≥28 weeks, or body length ≥35cm [273].
	Early fetal death: a death prior to the complete expulsion or extraction from its mother of a product of conception weighing 500-1,000g, equivalent to approximately 22-28 weeks' gestation; late fetal death: >1,000g or >28 weeks' gestation [240,275].
	A baby born with no signs of life ≥28 weeks' gestation [276].
ACOG/CDC/ NCHS	A spontaneous fetal death of ≥20 weeks' gestation or a weight of ≥350g [277,278].
RCOG	A baby delivered with no signs of life ≥24 weeks' gestation [281].

Abbreviations: CDC, Centers for Disease Control and Prevention; ICD-10, International Classification of Diseases-10th revision; NCHS, National Center for Health Statistics; RCOG, Royal College of Obstetricians & Gynaecologists; UNICEF, United Nations Children's Fund; WHO, World Health Organization.

2.7.4.1.2 Epidemiology

The miscarriage rate in high-income countries varies: 8-22% of clinically recognised pregnancies, i.e. from 5-6 weeks' gestation [283-288]. The rate is approximately 30% when taking into account early miscarriages of those pregnancies detected by human chorionic gonadotropin (hCG), i.e. before clinical recognition [284]. Data on miscarriage epidemiology in LMICs have been lacking due to several challenges: 1) most miscarriages occur outside of health facilities and are not registered; 2) most women initiate ANC late in the second trimester [7,81-84,289-291]; 3) less accurate estimation of gestational age due to limited access to ultrasound, and/or less reliable dating from the LMP due to limited literacy [92,292]; 4) induced abortion is illegal in most LMICs, thereby increasing the risk of misclassification of induced abortion as spontaneous miscarriage [293];

and 5) cultural and superstitious beliefs that may hinder pregnancy detection [289,294,295]. Approximately 14% of pregnancies ended in a miscarriage in India in 2015 [296] and 19% in Kenya between 2011 and 2013, a setting with high malaria and HIV prevalence [293].

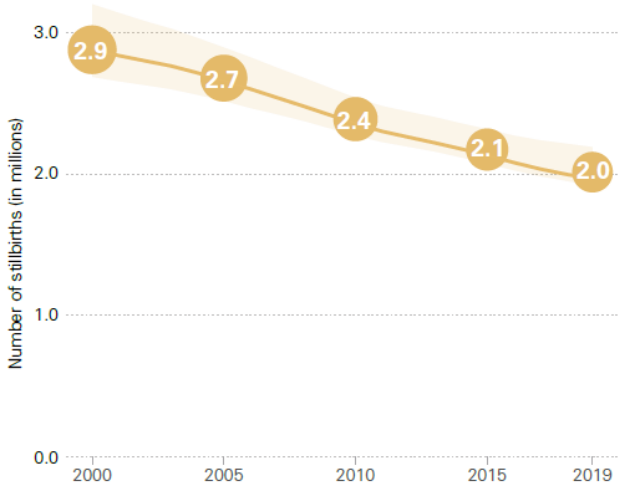


Figure 2.25. Global number of stillbirths, 2000-2019 (UNICEF 2020 [275]). Abbreviation: UNICEF, United Nations International Children's Emergency Fund.

Approximately 48 million stillbirths occurred globally in the past two decades. In 2019, an estimated two million babies were stillborn (Figure 2.25), with a global rate of 13.9 stillbirths per 1,000 total births. This corresponds to one stillbirth every 16 seconds. An additional 20 million stillbirths are projected to occur by 2030 [275]. The vast majority (84%) of stillbirths occur in LMICs, particularly sub-Saharan Africa (42%) and south Asia (34%), which account for more than three quarters of global stillbirths [275,297]. Between-country disparities in stillbirth rates are substantial (Figure 2.26), from 1.4 to 32.2 stillbirths per 1,000 total births. Of the 27 countries with a stillbirth rate >20, 22 are in sub-Saharan Africa. Approximately 42% of global stillbirths are intrapartum (Figure 2.27),

which could probably have been prevented with timely access to better quality care during pregnancy and birth [275].

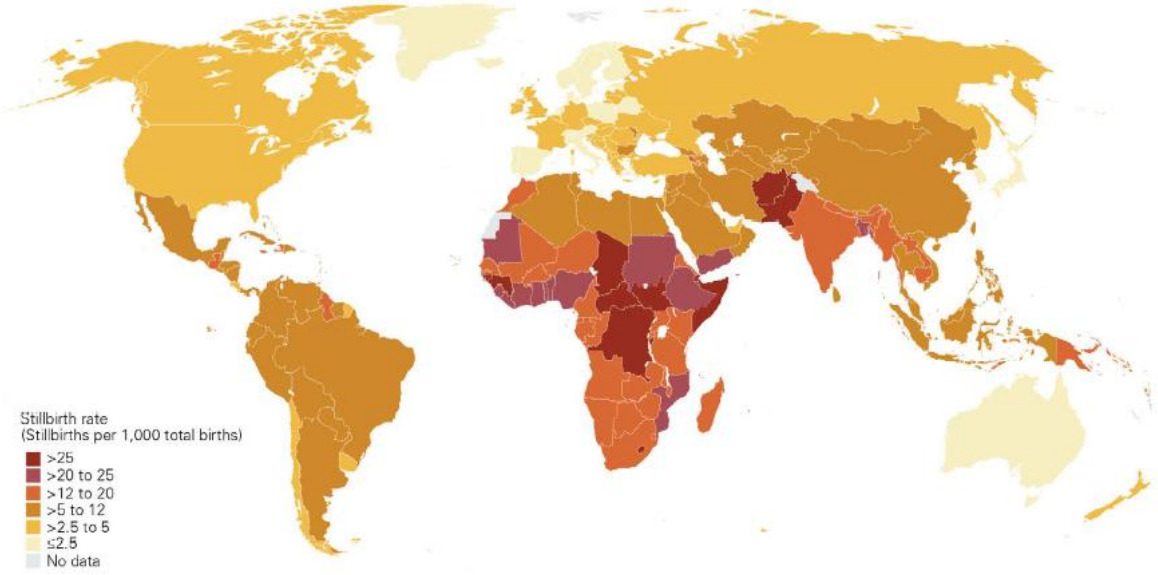


Figure 2.26. Stillbirth rates by country, 2019 (UNICEF 2020 [275]). Abbreviation: UNICEF, United Nations International Children's Emergency Fund.

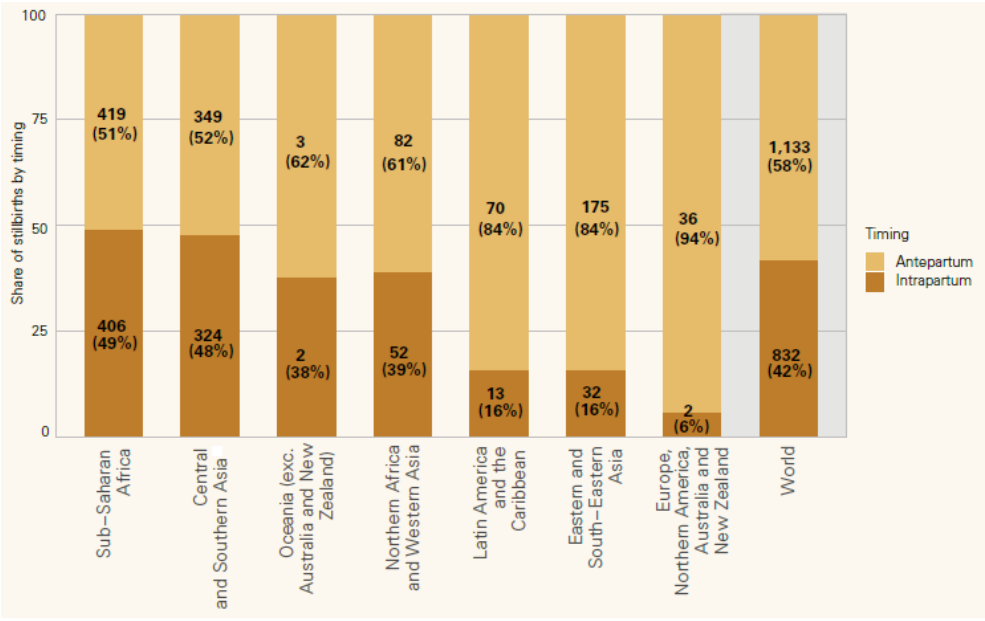


Figure 2.27. Proportion of antepartum and intrapartum stillbirths by Sustainable Development Goal region, 2019 (UNICEF 2020 [275]). The first number for each region corresponds to the number of stillbirths in thousands. Abbreviation: UNICEF, United Nations International Children's Emergency Fund.

Despite a 31% decline in the global number of stillbirths over the past two decades (Figure 2.25), sub-Saharan Africa did not exhibit this declining trend; there has even been a small increase in the number of stillbirths in this region (Figure 2.28). Approximately 0.8 million stillbirths occurred every year in sub-Saharan Africa between 2000 and 2019 (Figure 2.28). In 2000, 27% of all stillbirths worldwide occurred in sub-Saharan Africa, and this increased to 42% in 2019 [275].

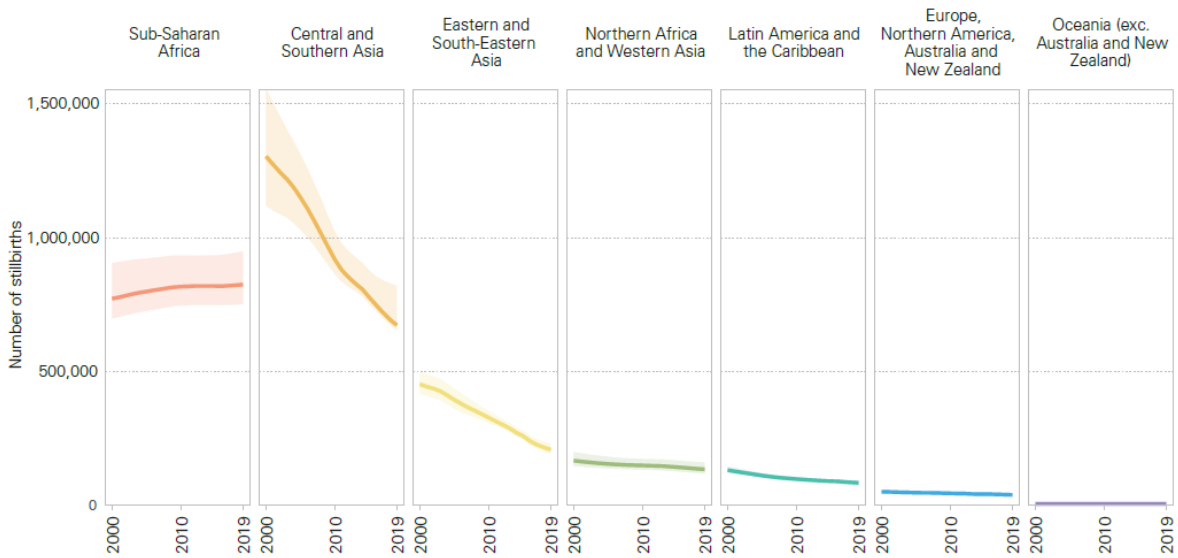


Figure 2.28. Number of stillbirths by Sustainable Development Goal region, 2000-2019 (UNICEF 2020 [275]). Abbreviation: UNICEF, United Nations International Children's Emergency Fund.

2.7.4.2 Neonatal deaths

Information on neonatal deaths is provided in 2.2.2 Perinatal health.

2.7.5 Fetal growth

2.7.5.1 Physiology of fetal growth

The interactions between the fetus, placenta and mother (Figure 2.29) are vital for fetal growth regulation. The placenta mediates the communication between the fetus and mother [298-302]. The interactions between the maternal genome and environment influence the woman's pre-pregnancy state (Figure 2.29). Several factors (e.g. co-morbidities, smoking, nutritional status and hypoxia) determine the maternal state in pregnancy [35,298,300-302] (Figure 2.29), see also perinatal health framework proposed by Misra et al. [35] (Figure 2.2). Placental trophoblast invasion stimulates increases in placental blood flow and growth and, in turn, the production of placental hormones and transporters to communicate and transfer nutrients/waste between the mother and fetus [298,301,302]. The placenta also controls the glucocorticoid balance between the two [298] (Figure 2.29). Placental hormones – e.g. hCG, lactogen, growth hormone (GH), insulin-like growth factor-1 (IGF-1), estrogens and progesterone – influence maternal conditions during pregnancy: uterine artery blood flow, metabolism and behaviour, and nutrient intake. These changes are essential to promote the growth and development of the placenta [298,301,302] (Figure 2.29). Competent placental function promotes fetal growth, whereas maternal constraint restricts fetal growth. Furthermore, fetal growth is influenced by the fetal genome [298,300-302] (Figure 2.29).

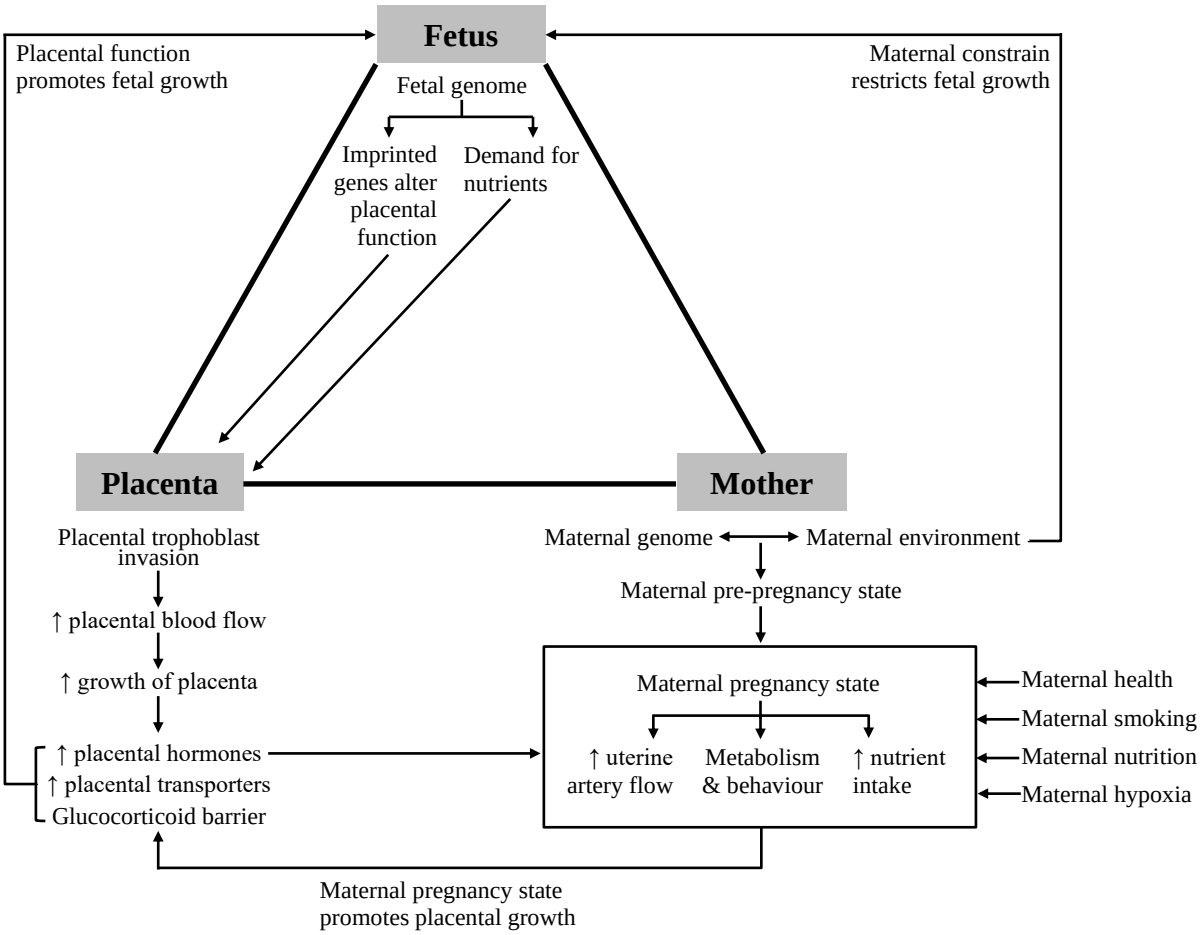


Figure 2.29. Interactions between the fetus, placenta and mother. Adapted from Murphy et al. [298]. See text for description.

2.7.5.2 Fetal biometry to assess fetal growth

2.7.5.2.1 Fetal biometry and estimated fetal weight

Ultrasound examination facilitates not only accurate pregnancy dating but also screening for fetal growth disorders by measuring fetal biometry. The most commonly measured fetal biometric parameters are biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL); these can be combined to calculate the estimated fetal weight (EFW) [303-309] (Table 2.12). The fetal biometric measurements should be performed in a standardised manner with strict adherence to the criteria needed to obtain each measurement, as shown by the INTERGROWTH-21st study [310,311]. The

measurement techniques for each biometry are provided in Chapter 7 and discussed thoroughly in the INTERGROWTH-21st Ultrasound Operations Manual, which can be found online (https://intergrowth21.tghn.org/). Fetal growth is a dynamic process; therefore, its assessment requires at least two ultrasound measurements taken from the same fetus at different gestational ages [312].

Table 2.12. Formulae used to estimate fetal weight.

Authors	Formula
Warsof et al.1977 [313]	$Log_{10}(EFW \text{ in kg}) = -1.599 + (0.144 \times BPD) + (0.032 \times AC) - (0.000111 \times AC \times BPD^2)$
Hadlock et al.1984 [314]	$Log_{10}(EFW) = 1.5115 + (0.0436 \times AC) + (0.1517 \times FL) - (0.00321 \times AC \times FL) + (0.0006923 \times BPD \times HC)$
Hadlock et al.1985 [315]	$Log_{10}(EFW) = 1.3596 - (0.00386 \times AC \times FL) + (0.0064 \times HC) + (0.00061 \times BPD \times AC) + (0.0424 \times AC) + (0.174 \times FL)$
INTERGROWTH-21st 2017 [308]	$Log(EFW) = 5.084820 - 54.06633 \times (AC/100)^3 - 95.80076 \times (AC/100)^3 \times \log(AC/100) + 3.136370 \times (HC/100)$
EFW is expressed in grams unless specified. Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; EFW, estimated fetal weight; FL, femur length; HC, head circumference; kg, kilogram;	

EFW is most commonly used to monitor fetal size and growth [312,316]. Several formulae (Table 2.12) have been proposed to estimate fetal weight [308,313-315]. However, there are several drawbacks of using EFW: 1) errors in the measurement of each fetal biometric parameter are multiplied [312]; 2) large intra- and inter-observer variability can compromise EFW accuracy, with errors ranging from 10-15% on average, which can be as high as 25% [317-319]; 3) fetuses with different phenotypes could have the same EFW, e.g. those with large HC and small AC may have the same EFW as those with small HC and large AC [312]; 4) most EFW formulae include AC (Table 2.12), which can be technically difficult to measure [312,320]; 5) the estimation assumes a uniform density of tissue; therefore, EFW could be overestimated in macrosomic fetuses with

relatively greater adipose tissue (less dense than lean body mass), and underestimated in growth-restricted fetuses with less adipose tissue [299].

2.7.5.2.2 Fetal growth standards versus fetal growth references

Prescriptive fetal growth standards are constructed based on prospectively collected data from the fetuses of healthy women living in geographically diverse regions who are at low risk of adverse maternal and perinatal outcomes (i.e. they describe fetal growth under optimal conditions), and whose pregnancies have been accurately dated with appropriate ultrasound protocols and quality control. By contrast, descriptive fetal growth references are developed based on populations of fetuses/infants from normal and complicated pregnancies, i.e. they describe the distribution of measures in a specific unselected population at a given time period. Fetal growth standards are preferable because they describe aspirational and biological norms achieved by healthy individuals and populations worldwide [299,312,316]. The first international, prescriptive, fetal growth standards were developed by the INTERGROWTH-21st Project [310] (Table 2.13), which applied the same methods and conceptual approach as the WHO Multicentre Growth Reference Study, which produced the WHO Child Growth Standards in 2006 [321]. More recently, WHO itself constructed fetal growth standards [322] (Table 2.13); however, as noted by the authors, their generalisability is limited by the small sample size. Lastly, the National Institute of Child Health and Human Development (NICHD) developed ethnic-specific fetal growth standards based upon what the authors described as significant differences in fetal growth amongst four ethnicities (White, Black, Hispanic and

Asian) in the USA [305] (Table 2.13). Therefore, this study [305] conflicts with the prescriptive “one standard fits all” concept [322,323].

It is imperative to understand the difference between prescriptive standards and descriptive references of fetal growth charts. Fetal growth standards are likely to produce a higher 3rd percentile of birth weight for gestational age than that produced by the fetal growth references at the same gestational age, because the latter was developed based on populations including fetuses from complicated pregnancies. Therefore, fetal growth references generally employ a higher centile cut-off to identify abnormal growth, e.g. 10th instead of 3rd percentile of birth weight for gestational age [299,312].

Table 2.13. Summary of the characteristics of studies aimed at developing fetal growth standards or references.

Authors	Country	Sample size (number recruited)	Design	Type of population	Type of sampling	Recruitment period	Chorionicity	Fetal measurements	Type of chart	Intended use
Jiang et al. 2013 [324]	China	6,832	Cross-sectional	Healthy population	Hospital based	>16 weeks	Singleton	BPD, AC, FL	Reference	Local
Papageorghiou et al. 2014 (Intergrowth-21st) [310]	International (UK, Italy, Brazil, USA, Oman, China, India, Kenya)	13,108	Longitudinal	Healthy population	Population based	9-14 weeks	Singleton	BPD, HC, AC, FL, OFD	Standards	International
Júnior et al. 2014 [325]	Brazil	31,476	Cross-sectional, retrospective	Healthy population	Hospital based	<14 weeks	Singleton	BPD, HC, AC, FL, EFW	Reference	Local
Buck Louis et al. 2015 (NICHD) [305]	USA (White, Black, Hispanic and Asian women)	2,334	Longitudinal	Healthy population	Hospital based	8-13 weeks	Singleton	BPD, HC, AC, FL, HL, EFW	Standards	International/ ethnic-specific
Stirrup et al. 2015 [326]	England	2,025	Retrospective	All inclusive	Hospital based	>14 weeks	Twin	BPD, HC, AC, FL	Reference	Local
Rizzo et al. 2016 [327]	Italy	8,070	Retrospective	All inclusive	Hospital based	First trimester	Singleton	BPD, HC, AC, FL	Reference	Local/sex-specific
Gabbay-Benziv et al. 2017 [328]	USA	2,161	Retrospective	All inclusive	Hospital based	<20 weeks	Twin	EFW	Reference	Local
Kiserud et al. 2017 (WHO) [322]	International (Argentina, Brazil, DR Congo, Egypt, Denmark, France, Germany, India, Norway, Thailand)	1,387	Longitudinal	Healthy population	Hospital based	First trimester	Singleton	BPD, HC, AC, FL, HL, EFW	Standards	International

Adapted from Ohuma et al. [323].
Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; DR Congo, Democratic Republic of Congo; EFW, estimated fetal weight; FL, femur length; HC, head circumference; HL, humeral length; NICHD, National Institute of Child Health and Human Development; OFD, occipitofrontal diameter;UK, United Kingdom; USA, United States of America; WHO, World Health Organization.

2.7.5.2.3 Assessment of fetal growth

Ideally, the assessment of fetal growth is based on serial ultrasound measurements of biometric parameters collected in a longitudinal fashion, which allows the evaluation of fetal growth rates and trajectories. Serial scans can be used to assess the interval growth in order to identify fetuses departing from an optimal growth trajectory. However, there is no consensus definition of what constitutes a 'normal' fetal growth velocity at any given gestational age for each biometric parameter. Intra- and inter-observer variability may compromise the accuracy of biometric measurements and, in turn, interval growth [329]. This is particularly true when the time interval between measurements is short, i.e. ≤2 weeks [330]. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommends that serial scans for interval growth should be performed at least three weeks apart [312]. Furthermore, serial third-trimester scans have been shown to be useful for the detection of fetal growth disorders [331-333]; however, this remains unclear for serial scans in the earlier trimesters [312].

To describe fetal size and growth, ISUOG recommends the use of the following terms: AGA, SGA, LGA, and early and late-onset IUGR. The definitions of these terms are provided in Table 2.14. SGA neonates are not necessarily growth-restricted *in utero*, i.e. constitutionally small. Suspected IUGR fetuses will not necessarily be SGA at birth, and fetuses may be growth-restricted despite not being SGA at birth [312].

Table 2.14. Definitions of terms used to describe fetal size and growth according to ISUOG.

Term	Definition
AGA	Individual biometric parameters and/or EFW between the 10th and 90th percentiles.
SGA	Fetal size is below a predefined threshold for its gestational age, typically EFW or AC <10th percentile; other cut-offs have also been used in the literature: 5th centile, 3rd centile, -2SD and Z-score deviation.
LGA	Fetal size is above a predefined threshold for its gestational age, typically EFW or AC >90th percentile; other cut-offs have also been used in the literature: 95th centile, 97th centile, +2SD and Z-score deviation.
IUGR	A fetus that has not achieved its growth potential.
	Early IUGR: <32 weeks' gestation, in the absent of congenital anomalies: AC/EFW <3rd centile or UA-AEDF Or 1. AC/EFW <10th centile combined with 2. UtA-PI >95th centile and/or 3. UA-PI >95th centile
	Late IUGR: ≥32 weeks' gestation, in the absent of congenital anomalies: AC/EFW <3rd centile Or at least two out of three of the following 1. AC/EFW <10th centile 2. AC/EFW crossing centiles >2 quartiles on growth centiles 3. CPR <5th centile or UA-PI >95th centile

Abbreviations: AC, abdominal circumference; AEDF, absent end-diastolic flow; AGA, appropriate for gestational age; CPR, cerebroplacental ratio; EFW, estimated fetal weight; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; IUGR, intrauterine growth restriction; LGA, large for gestational age; PI, pulsatility index; SD, standard deviation; SGA, small for gestational age; UA, umbilical artery; UtA, uterine artery.

2.7.5.3 Risk factors for fetal growth disorders

Risk factors for restricted and excessive fetal growth include potential abnormalities/conditions in the three "compartments": mother, fetus and placenta [299,300,334-336] (Table 2.15). Some risk factors for restricted fetal growth may affect more than one compartment [337] (Figure 2.30).

Table 2.15. Risk factors for restricted and excessive fetal growth.

	Risk factors
Maternal	**Restricted fetal growth** *Socio-demographic*: extreme age, ethnicity, lower socio-economic status. *Behavioural/environmental*: smoking, alcohol, illicit drug use, eating disorders, high altitude (i.e. chronic hypoxia). *Nutritional*: low pre-pregnancy weight, poor gestational weight gain. *Obstetrical*: poor antenatal care, multiple pregnancy, short inter-pregnancy interval, history of small for gestational age. *Systemic diseases*: chronic and gestational hypertension, anaemia, renal diseases (e.g. nephrotic syndrome), pulmonary disease, autoimmune diseases (e.g. antiphospholipid syndrome, systemic lupus erythematosus), gastro-intestinal diseases (e.g. Crohn's disease, ulcerative colitis, malabsorption). *Infections*: viral (e.g. human immunodeficiency virus, cytomegalovirus, varicella zoster), parasitic (e.g. malaria, toxoplasmosis). *Others*: constitutionally small, artificial reproductive technologies, uterine factors (e.g. fibroid, müllerian anomalies), maternal periodontal disease, medications (e.g. anticonvulsants, beta blockers, antiretrovirals), angiotensin gene mutation.
	Excessive fetal growth Pre-gestational and gestational diabetes, obesity.
Fetal	**Restricted fetal growth** *Genetic*: trisomy 21/18/13, Turner's syndrome, deletion of chromosome 4/5/13/18, ring chromosome structural alterations, uniparental disomy of chromosome 6/14/16. *Congenital malformations*: congenital heart disease, congenital diaphragmatic hernia, abdominal wall defects (e.g. omphalocele, gastroschisis), renal agenesis/dysplasia, anencephaly, single umbilical artery.
	Excessive fetal growth Fetal hyperinsulinemia associated with Beckwith–Wiedemann syndrome.
Placental	**Restricted fetal growth** *Placenta*: placental abruption/infarction/hemangioma/chorioangioma, placenta accreta, circumvallate placenta, confined placental mosaicism, diffuse chronic villitis, fetal villous obliteration. *Umbilical cord*: velamentous cord insertion, single umbilical artery.

2.7.5.4 Complications associated with fetal growth disorders

Fetal growth abnormalities are associated with increased risks of both short- and long-term complications. For short-term complications, perinatal death is associated with restricted fetal growth, whereas birth trauma is associated with excessive fetal growth. Other neonatal morbidities – including cerebral palsy, polycythaemia, hyperbilirubinaemia and hypoglycaemia – are associated with both restricted and excessive fetal growth. The associations between restricted fetal growth and long-term outcomes (e.g. adult-onset hypertension and diabetes mellitus) remain speculative [229,331-333].

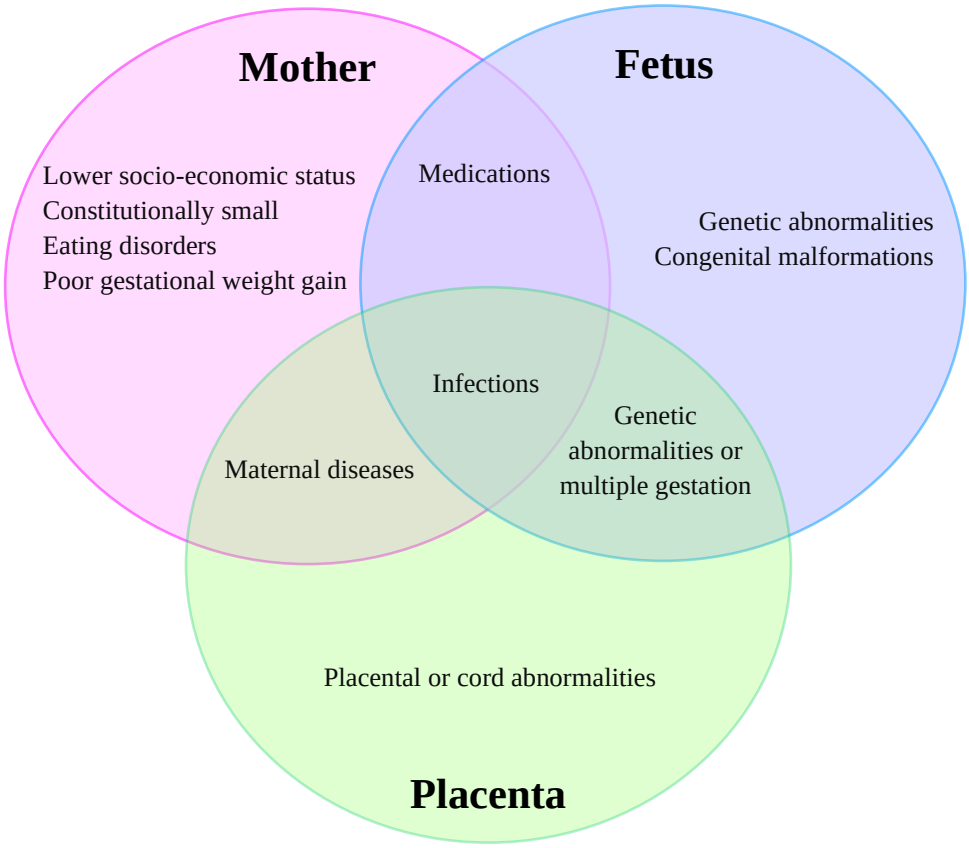


Figure 2.30. Risk factors for restricted fetal growth. Adapted from Cunningham et al. [337].

2.8 Soweto, South Africa

2.8.1 Population

Soweto (an acronym of *So*uth-*We*stern *To*wnship) is a township on the south-western part of Johannesburg, Gauteng Province, South Africa (Figure 2.31). Soweto is predominantly urban and peri-urban with low income and limited educational and employment opportunities. It has the highest population density of any district of Johannesburg: 6,135 people per km^2 in 2015 [338] (Figure 2.32).

Figure 2.31. Map of South Africa showing the nine provinces (A) and map of Gauteng Province showing Soweto and other cities (B). Adapted from Coulson et al. [339] and Stadler et al. [340].

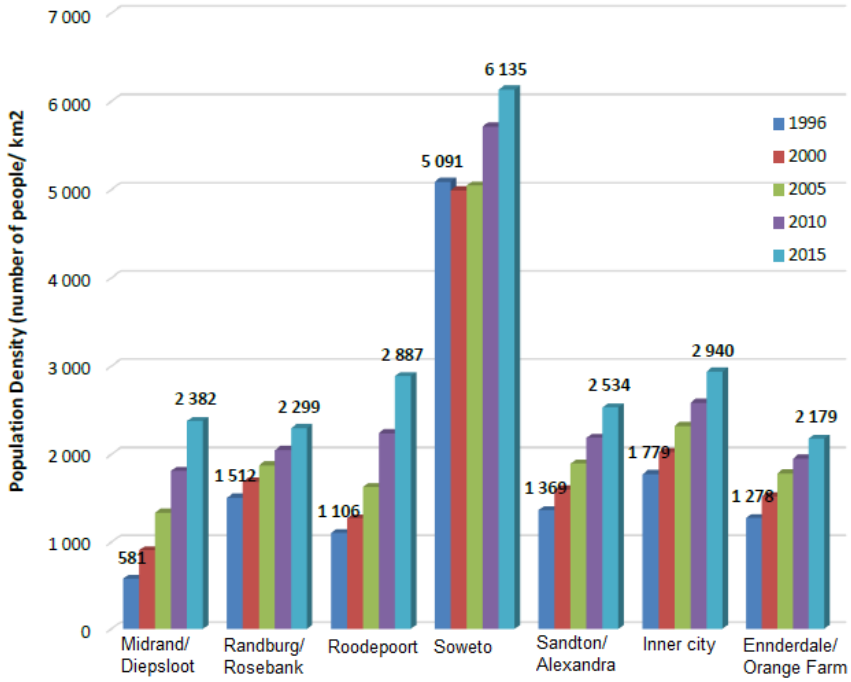


Figure 2.32. Population densities of Johannesburg by region, 1996-2015. Adapted from Annual Economic Review of the city of Johannesburg 2016 [338].

Gauteng is the smallest, yet most populated province (Figure 2.33). Approximately 15.5 million people (26%) out of South Africa's estimated population of 59.6 million in 2020 were living in this province. Gauteng, Kwazulu-Natal and Western Cape accounted for more than half (57.1%) of the total population (Figure 2.33). Approximately 51.1% (30.5 million) of the South African population in 2020 were female; 62.3% (37.2 million) were youths and adults aged 15-59, and the highest proportion of this age group was seen in Gauteng (67%). South Africa's population had grown by approximately 0.8 million between 2019 (58.8 million) and 2020 (59.6 million); this was mainly driven by births (births: +1.17 million, net migration: +0.17 million, deaths:-0.52 million). In 2020, on average, a South African woman gave birth to 2.33 children in her lifetime [341].

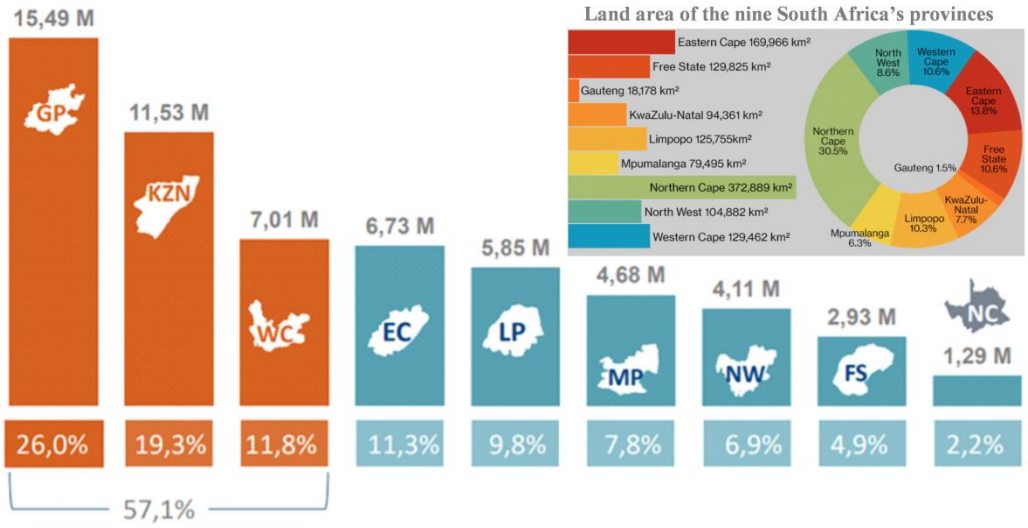


Figure 2.33. 2020 population estimates and land area by South Africa's province. Adapted from Maluleke et al. [341].

2.8.2 HIV epidemiology

South Africa has the largest HIV epidemic worldwide with an estimated 7.8 million HIV-positive people (13% of the population) in 2020, accounting for 20% of the global HIV prevalence [1,341]. Although the epidemic is generalised, Black African women of childbearing age are at high risk for HIV (Figure 2.34) [342]; a prevalence of 31.6% has been reported among Black African women aged 20-35 [343]. Among women aged 15-49, South Africa contributes 25% of the global HIV prevalence (Figure 2.35) [1] and 22% of the global new HIV infections [2]. Among women aged 15-24, South Africa accounted for 28% of the global new HIV infections in 2019 [2]. South African women aged 15-24 are three times more likely to be HIV-positive than men in the same age group: incidence 1.51% versus 0.49% [342]. These women will likely become pregnant and give birth while they are HIV-positive.

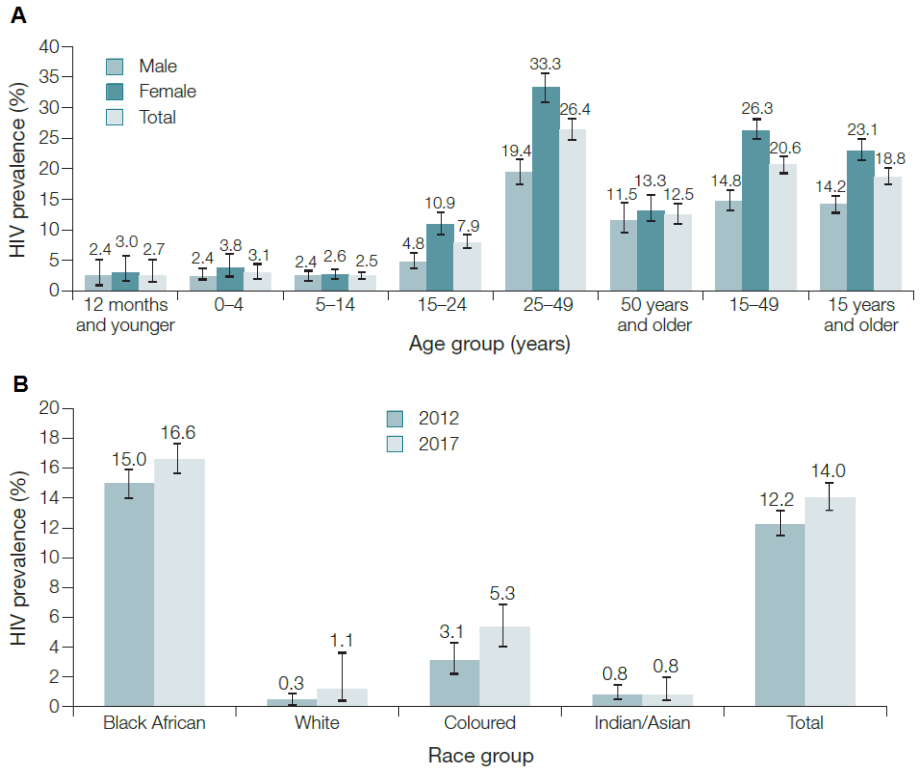


Figure 2.34. South Africa's HIV prevalence by age groups and sex (A) and race (B), 2017 (Simbayi et al. [342]).

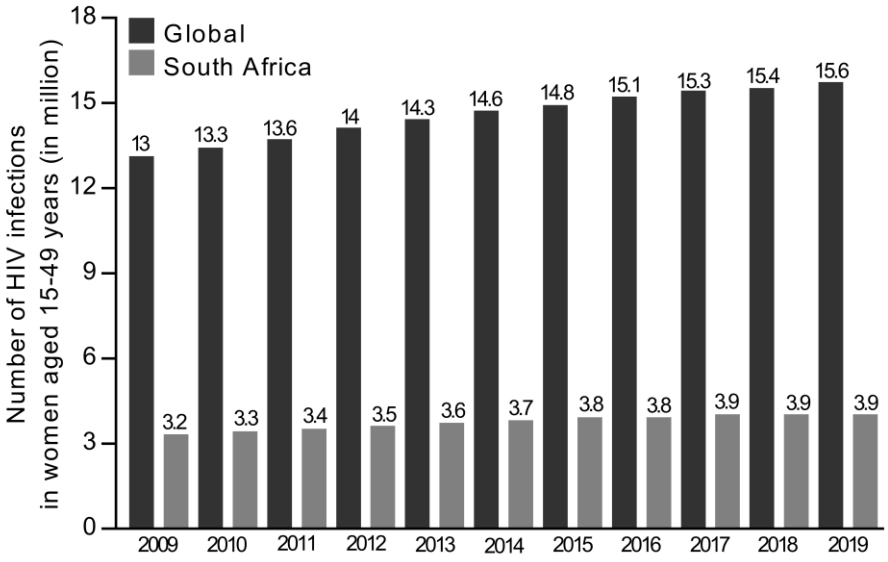


Figure 2.35. Number of HIV infections in women of reproductive age worldwide and in South Africa (UNAIDS 2020 [1]). Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; UNAIDS, The Joint United Nations Programme on HIV/AIDS.

HIV/AIDS remains the leading cause of death in South Africa (Figures 2.36) [344-347]. The highest number of AIDS-related mortalities was in 2006 (286,588 deaths); this number had steadily declined and stood at 126,805 deaths in 2019. This decline is attributed to the expansion of ART coverage over time, starting in 2005 [348].

1997 leading causes of death	Deaths (%)	Years of life lost (%)	Age-standardised death rates (per 100 000)	2012 leading causes of death	Deaths (%)	Years of life lost (%)	Age-standardised death rates (per 100 000)	Change in age-standardised death rates* (%)
Persons				Persons				
1 HIV/AIDS	60 336 (14·5%)	1 539 958 (18·8%)	145	1 HIV/AIDS	153 661 (29·1%)	3 576 809 (35·7%)	319	120·1%
2 Cerebrovascular disease	31 472 (7·6%)	410 876 (5·0%)	111	2 Cerebrovascular disease	39 830 (7·5%)	476 955 (4·8%)	110	–0·8%
3 Interpersonal violence	30 569 (7·3%)	763 455 (9·3%)	74	3 Lower respiratory infections	25 977 (4·9%)	464 304 (4·6%)	61	–0·5%
4 Tuberculosis	26 344 (6·3%)	513 762 (6·3%)	80	4 Ischaemic heart disease	24 969 (4·7%)	306 181 (3·1%)	69	–19·0%
5 Ischaemic heart disease	23 813 (5·7%)	298 058 (3·6%)	85	5 Tuberculosis	23 817 (4·5%)	461 024 (4·6%)	55	–31·0%
6 Lower respiratory infections	21 908 (5·3%)	430 368 (5·2%)	62	6 Diabetes	18 894 (3·6%)	255 509 (2·5%)	51	29·3%
7 Diarrhoeal diseases	18 737 (4·5%)	463 227 (5·6%)	44	7 Hypertensive heart disease	18 755 (3·5%)	209 219 (2·1%)	53	–6·7%
8 Hypertensive heart disease	15 771 (3·8%)	188 653 (2·3%)	57	8 Interpersonal violence	18 741 (3·5%)	460 180 (4·6%)	35	–52·0%
9 Road injuries	15 159 (3·6%)	368 912 (4·5%)	38	9 Road injuries	17 597 (3·3%)	422 715 (4·2%)	35	–8·9%
10 Diabetes	11 321 (2·7%)	166 014 (2·0%)	40	10 Diarrhoeal diseases	16 349 (3·1%)	369 289 (3·7%)	34	–22·7%
Top 10 causes	255 430 (61·4%)	5 143 283 (62·7%)	734	Top 10 causes	358 590 (67·8%)	7 002 185 (69·8%)	823	
Total	**416 209 (100·0%)**	**8 203 564 (100·0%)**	**1215**	**Total**	**528 947 (100·0%)**	**10 032 887 (100·0%)**	**1232**	**1·4%**

Figure 2.36. Top ten causes of death, years of life lost and age-standardised death rates in South Africa, 1997 and 2012 (Pillay-van Wyk et al. [344]).

2.8.3 HIV and antiretroviral therapy in the context of pregnancy

More pregnant women in South Africa know their HIV status at their first ANC visit (Figure 2.37) and >30% are HIV-positive [349,350]. Every year 320,000 HIV-positive women in the country become pregnant, which represents 23% of the global number (1.4 million); this figure is the highest in the world [3,350]. More than 97% of these women receive HAART for PMTCT [3]. South African PMTCT guidelines [351-354] follow the WHO recommendations (Table 2.4); additional information on these guidelines is provided in the relevant analysis chapter: Chapter 5.

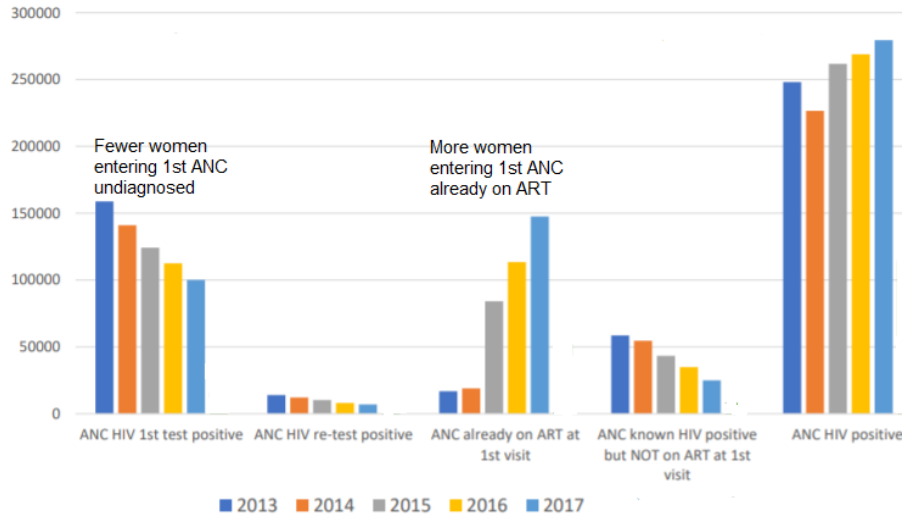


Figure 2.37. Antenatal HIV testing in South Africa, 2013-2017 (Myer et al. [349]). Abbreviations: ANC, antenatal care; ART, antiretroviral therapy.

South Africa has been successful in PMTCT, as shown by a nearly 80% reduction in MTCT rate between 2010 and 2019, from 16% to 3.3% [3]. This achievement is partly attributed to improvements in ART regimens and coverage. The potency of ART regimens has been increased from single-dose NVP to lifelong HAART (Table 2.4). ART coverage has been improved by: 1) broadening the eligibility criteria for PMTCT from CD4 <200 to CD4<350 or <500 cells/mm^3 and, in turn, universal ART (Table 2.4), and 2) increasing the roll-out of ART. In 2010, only 70% of HIV-positive pregnant women received ART; this figure increased to >97% in 2019 [3]. Figure 2.37 shows that more pregnant women are already on ART at their first ANC visit [349].

2.9 Maternal HIV, ART and perinatal outcomes

By mid-2020, 185 countries had adopted the "treat all" recommendation [32]. This suggests that more HIV-positive pregnant women have been initiating ART pre-conception and have, therefore, had longer *in utero* exposure to a combination of at least three antiretrovirals, i.e. HAART [12] (Table 2.4). However, the effects

of maternal HIV/ART on perinatal outcomes, which mainly rely on observational studies, remain unclear. Existing studies have shown inconsistent findings as to whether HAART increases the risk of PTB, LBW and SGA compared with monotherapy [13-23]. The findings have also been inconsistent regarding whether PI-based ART [25,26] and pre-conception initiation [18,24] are associated with an increased risk of PTB compared with non PI-based ART and post-conception initiation.

The inconsistent associations between maternal HIV/ART and perinatal outcomes are partly attributed to the nature of observational studies, which are prone to bias. In addition, small sample sizes and the rarity of outcome events (e.g. stillbirth and NND) might have contributed to the limited statistical power and biased estimates [17-23]. A large randomised controlled trial (RCT) should be an ideal study design to investigate the effects of ART on perinatal outcomes. However, this is hindered by an ethical issue of enrolling pregnant women in most RCTs of ART [27], and by funding restrictions particularly for LMICs where >90% of HIV-positive women reside [355]. Despite differences in study designs and populations and other concurrent risk factors across studies, pooling observational studies through a meta-analysis should be advantageous. Meta-analysis may also be beneficial from a power perspective particularly for rare outcome events, and for newer ART regimens (e.g. DTG-based ART) with limited safety data in pregnancy [222].

The inconsistent associations mentioned above could also be a result of misclassification of adverse perinatal outcomes (e.g. PTB, SGA) due to less

accurate estimates of gestational age using newborn clinical assessment [13], LMP [13-20], SFH [13,15,17], and/or late ultrasound [13,15,17,19]. Lack of ultrasound and delayed first ANC are the main reasons limiting accurate gestational age estimation by first-trimester ultrasound, particularly in sub-Saharan Africa and south Asia (see 2.3 Determination of gestational age).

Maternal HIV and ART are not the only predictors of adverse perinatal outcomes. It is therefore imperative to identify maternal risk factors (other than HIV and ART) that may contribute to the occurrence of adverse perinatal outcomes, as an attempt to provide guidance for targeting improvement of newborn's health. For risk factors identification, perinatal outcomes should not overlap each other. An overlap between two perinatal outcomes suggests that they define the vast majority of the same babies, i.e. they are not worth differentiating in risk factor analysis. It is, therefore, necessary to perform an overlap analysis between perinatal outcomes, which requires accurate information on gestational age and birth weight so as to minimise the misclassification.

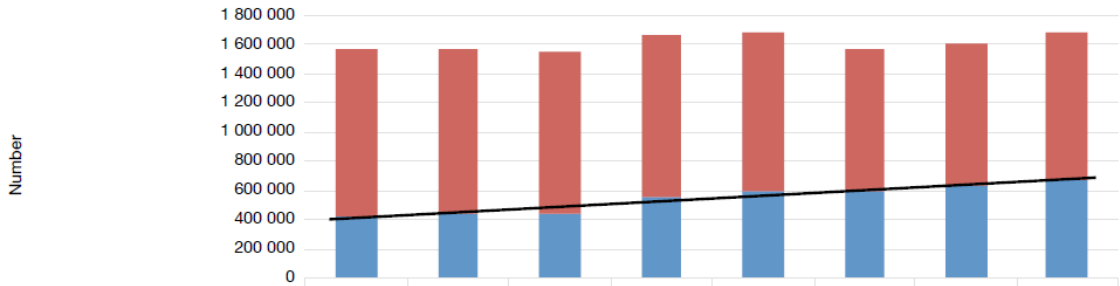
As shown in Figure 2.30, maternal infections and medications (including HIV and ART) during pregnancy may compromise not only the mother, but also the fetus and placenta – the three main factors regulating fetal growth. However, to date, no studies have been conducted to assess whether maternal HIV/ART influences fetal growth patterns. This requires longitudinal measurements of fetal biometric parameters (BPD, HC, AC and FL) from 14 weeks' gestation onwards [312]. The challenges of such a longitudinal study are the high cost, longer data collection period, need for trained and dedicated ultrasonographers, and more importantly

strong maternal compliance. These could be challenging for both low and middle-income (with limited ultrasound availability and delayed first ANC) and high-income countries.

2.9.1 South African context

Ongoing surveillance for the safety of *in utero* ART exposure should become a priority in South Africa, a country with the largest HIV epidemic worldwide, and more importantly, the highest number of HIV-positive pregnant women on lifelong HAART. However, this country still faces several challenges. First, accurate gestational age estimation remains challenging due to limited access to ultrasound and/or delayed first ANC [13,14,28-30,356,357]. Approximately 32% and 82% of women in urban and rural areas of South Africa, respectively, do not have access to ultrasound [358]. Furthermore, South African studies showed that the majority of women (up to 89%) present at their first ANC in the second trimester, and they do not routinely receive an ultrasound scan [13,29,357]. The national data show an increasing trend in the number of ANC first visits <20 weeks' gestation [359] (Figure 2.38). Despite the WHO recommendation for a dating scan <24 weeks' gestation [78], ACOG and ISUOG suggest that scans after 14 weeks' gestation may compromise gestational age accuracy [79,312]. So far, in the context of maternal HIV, studies in which all women are accurately dated using a first-trimester scan have never been conducted in South Africa and other sub-Saharan African countries. Second, whilst newborns should be weighed within 24h of birth, i.e. before significant weight loss [360], in most South African studies, birth weight is measured up to several days after birth or simply captured from medical records [13,14,28-31]. Third, the number of ANC visits

throughout pregnancy remains low in South Africa. The national estimates indicate that, in 2019-2020, 83% of South African women visited an antenatal health facility at least once in pregnancy [347]. However, only 25% of South African women receive at least four ANCs [14]. An adequate number of ANCs – eight as per WHO's recommendation [78] – is necessary to ensure the best health conditions for both the mother and baby, and to monitor fetal growth when ultrasound is available.



	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18
Antenatal 1st visit - total	1 140 788	1 126 592	1 099 389	1 108 077	1 093 391	978 170	979 532	1 013 796
Antenatal 1st visit before 20 weeks	425 059	452 423	446 269	551 109	588 012	598 935	638 710	675 305

Figure 2.38. Trends in number of antenatal first visit before 20 weeks' gestation in South Africa, 2010-2018 (Massyn et al. [359]).

These issues highlight the need to conduct a prospective longitudinal study in South Africa, in which: 1) all women are recruited before 14 weeks' gestation; 2) gestational age is determined using a first-trimester ultrasound; 3) birth weight is directly measured using a standardised procedure within 24h of birth; and 4) women are requested to perform serial antenatal visits, which facilitates the repeated measurements of fetal biometry throughout pregnancy. With these in place, I have been able to perform the first ever analysis of perinatal outcomes using accurately determined gestational age and birth weight in HIV settings in sub-Saharan Africa. The repeated measurements of fetal biometry allow the

present thesis to assess differences in fetal growth patterns by maternal HIV/ART, which has never been conducted in any settings.

Chapter 3: Antiretroviral therapy and adverse perinatal outcomes: a systematic review and meta-analysis.

3.1 Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that, globally, 18.8 million women aged 15 years and over were living with HIV in 2018 [361], of whom 1.3 million were pregnant [362]. HIV-positive pregnant or breastfeeding women can transmit HIV to their fetuses or infants; without any intervention, mother-to-child transmission (MTCT) rates range from 15% to 45% [363]. In the absence of any treatment, 52.5% of HIV-positive and 7.6% of HIV-negative children born to HIV-positive mothers die by the age of 2 years in Africa [364].

The current guidelines on the use of antiretroviral therapy (ART) in pregnancy, developed by the World Health Organization (WHO), recommend immediate initiation of lifelong efavirenz (EFV)-based highly active antiretroviral therapy (HAART) for all HIV-positive pregnant women irrespective of clinical and immunological status – the so-called "treat all" recommendation [12]. The use of ART during pregnancy reduced new paediatric HIV infections (aged 0–14 years) by approximately 64% between 2000 and 2018, from 450,000 to 160,000 [60]. Furthermore, antenatal ART has decreased AIDS-related maternal mortality by

49%, from 530,000 deaths in 2000 to 270,000 in 2018 [11]. Given these benefits, ART coverage to prevent MTCT (PMTCT) of HIV has been expanded. Approximately 44% of HIV-positive pregnant women worldwide received ART in 2010, which rose to 82% in 2018 [61]. The "treat all" recommendation and the rapid global scale-up of ART coverage have resulted in an increased proportion of women on ART prior to conception and so babies are being increasingly exposed to longer periods of *in utero* ART. However, safety data about the effects of *in utero* ART exposure on perinatal outcomes are scarce due to the exclusion of pregnant women from most randomised controlled trials (RCTs) [27,65]. Therefore, ongoing surveillance for the safety of *in utero* ART exposure is crucial.

A meta-analysis has shown an association between untreated maternal HIV infection and an increased risk of preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA) and stillbirth compared with HIV-negative women – a finding that was attributed to HIV-related poor maternal health [365]. However, a meta-analysis comparing the risk of adverse perinatal outcomes in treated HIV-positive versus HIV-negative women has never been conducted. This comparison remains crucial to understand whether the previously observed differences in perinatal outcomes in ART-naïve HIV-positive and HIV-negative women [365] have been narrowed by the global expansion of ART coverage.

The comparison of perinatal outcomes in HIV-positive pregnant women receiving ART versus those not receiving ART provides the best evidence to assess the effect of *in utero* ART exposure. A systematic review and meta-analysis published in 2007 showed no difference in the risk of PTB of HIV-positive

pregnant women on ART [62]. However, this meta-analysis included only six cohorts whose participants were recruited between 1990 and 2003 [62]. Since 2003, the WHO guidelines on antenatal ART have been updated four times: in 2006 [57], 2010 (option A and option B) [58], 2013 (option B+) [59], and 2015 ("treat all") [12]. Many studies implementing these guidelines have been conducted [14,18,19,22,28,30,366-376], which were not included in the meta-analysis [62]. In addition, PTB was the only perinatal outcome reported [62].

Current evidence remains uncertain whether different ART complexity and class, and timing of ART initiation have different impact on perinatal outcomes. Regarding ART complexity, several studies have shown that HAART is associated with an increased risk of PTB [15,18-20], LBW [16] and SGA [15] compared with monotherapy; however, other studies did not observe such associations [13,14]. Approximately 23 low and middle-income countries (LMICs), where more than 90% of HIV-positive pregnant women reside, have adopted the WHO-recommended lifelong EFV-based HAART [377]. However, there is no systematic review to date that has specifically assessed the risk of adverse perinatal outcomes by ART complexity (monotherapy, dual therapy and HAART).

The advent of potent protease inhibitor (PI)-based ART has raised concerns about the safety of this ART class in pregnancy. An earlier meta-analysis showed that PTB was significantly more frequent in HIV-positive pregnant women receiving PI-based ART than in women receiving non PI-based ART [62]. However, this meta-analysis only included eight cohorts recruited between 1998 and 2004 [62].

A more recent meta-analysis published in 2016 also showed an increased risk of PTB in women on PI-based ART compared with women on non PI-based ART [63]. However, this meta-analysis included 10 studies with three different definitions of PTB: <36 weeks' [378], <37 weeks' [26,371,372,379-383] and ≤37 weeks' gestation [25], which might have resulted in misclassification bias. Furthermore, these two meta-analyses [62,63] only included PTB as the outcome of interest.

The influence of different timing of ART initiation on perinatal outcomes was recently assessed by a meta-analysis of 11 cohorts published up to 2016 [64]. This meta-analysis observed a higher risk of PTB, very preterm birth (VPTB) and LBW in HIV-positive women initiating pre-conception versus post-conception ART [64]. Nevertheless, this meta-analysis was unable to show which class of ART significantly increased the risk of PTB, VPTB and LBW if initiated before conception, i.e. whether only PI-based or non-PI-based ART or both classes [64]. The analysis of VPTB in this meta-analysis [64] included a total of 9,772 women, 89% (n=8,678) of whom were captured from a single study [152] that defined VPTB differently to the protocol, which might have contributed to misclassification bias. Furthermore, this meta-analysis [64] was unable to assess the risk of adverse perinatal outcomes in women starting ART in the first-trimester versus women starting after first-trimester.

All studies included in the previous systematic reviews and meta-analyses [62,64] were observational and, therefore, prone to bias because the groups compared might have been different in characteristics other than ART-related factors.

Confounding factors, such as maternal age, smoking, alcohol consumption, history of adverse perinatal outcomes, maternal viral load and CD4 count might have been responsible for adverse perinatal outcomes. However, none of these reviews [62,64] performed the meta-analysis of adjusted effect estimates controlling for relevant confounding factors.

This chapter explores the effects of maternal HIV/ART, antenatal ART, different ART complexity and class, and different timing of ART initiation on perinatal outcomes, using a systematic review and meta-analysis of both unadjusted and adjusted effect estimates.

3.2 Aims

This chapter is aimed at assessing:

1. The effect of maternal HIV/ART on perinatal outcomes, by comparing the risk in treated HIV-positive versus HIV-negative pregnant women.
2. The effect of maternal ART on perinatal outcomes, by comparing the risk in treated HIV-positive versus untreated HIV-positive pregnant women.
3. The effect of ART complexity on perinatal outcomes, by comparing the risk in treated HIV-positive pregnant women receiving different ART complexities: monotherapy, dual therapy and HAART.
4. The effect of ART class on perinatal outcomes, by comparing the risk in treated HIV-positive pregnant women receiving different ART classes: PI and non PI.
5. The effect of timing of ART initiation on perinatal outcomes, by comparing the risk in treated HIV-positive pregnant women with different timings of

ART initiation: pre-conception and post-conception (first-trimester and after first-trimester).

3.3 Methods

3.3.1 Search strategy

The study background, rationale and methods were specified in advance in a protocol (Appendix 3.1) developed using the Cochrane review guidelines [384]. The present study is under the umbrella of a systematic review project focusing on adverse perinatal outcomes in HIV-positive pregnant women on ART. Before conducting any review, the protocol was registered online at the international prospective register of systematic reviews (PROSPERO number CRD42013005637) [385]. Literature searches were conducted systematically by a specialist librarian (SK) in five general electronic scientific 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 registry), for studies published between 01 January 1980 and 28 April 2018. The search terms included “HIV”, “antiretroviral therapy”, “pregnancy outcome” (as a general term) and specific terms related to pregnancy outcomes: “preterm birth”, “intrauterine growth restriction”, “small for gestational age”, “low birth weight”, “miscarriage”, “stillbirth” and “neonatal death”. In the search strategy, a combination of free-text terms (e.g. preterm birth), word variants (e.g. intra-uterine and intrauterine), synonyms (e.g. neonatal death and neonatal loss) and controlled vocabulary terms (MeSH and Emtree) was used together with the

Boolean “AND” and “OR” operators to identify the relevant studies. No methodology and language filters were applied; studies from all countries were eligible; full-text articles and abstracts were considered.

A comprehensive search strategy was conducted in two steps: “specific” and “general” search, so as to ensure no studies were missed. The “specific” search was aimed at capturing studies assessing “(preterm birth or intrauterine growth restriction or small for gestational age or low birth weight or miscarriage or stillbirth or neonatal death) and (HIV or antiretroviral therapy)” (Appendix 3.2). The “general” search was aimed at capturing studies assessing “(pregnancy outcome) and (HIV or antiretroviral therapy)” (Appendix 3.3). The search strategies provided in Appendix 3.2 and Appendix 3.3 were used to search Embase via OVID and adapted for: 1) all literature and trial electronic databases; 2) search of conference abstracts (see below). All retrieved articles were imported into EndNote™ X6 reference manager (Clarivate Analytics, Philadelphia, USA).

In order to find the most recent relevant studies, one reviewer (WS) searched conference abstracts from selected international symposia on HIV/AIDS conducted between 2013 and 2018, including the International AIDS Conference, the International AIDS Society Conference on HIV Science (IAS), the Conference on Retroviruses and Opportunistic Infections (CROI) and the HIV Research for Prevention (HIVR4P) conference. The specific terms related to pregnancy outcomes (Appendix 3.2) were used to find abstracts in published abstract books. The exercise was conducted using Adobe Acrobat™ Pro XI version (Adobe Inc.,

California, USA), which allows the use of multiple words or phrases as search terms.

Hand searches of references of all included studies were also conducted to identify additional citations. Authors were contacted if full-text articles did not provide sufficient information.

3.3.2 Study selection and data extraction

3.3.2.1 Study selection

Two independent reviewers screened the titles and abstracts of all retrieved articles to identify potentially relevant articles. The same reviewers then independently screened full-text versions of those articles using the following inclusion criteria:

- **Study design**: Retrospective and prospective cohorts, case-control and cross-sectional studies. RCTs were not included in the present review because these studies were used by another member of our research group for a network meta-analysis of RCTs investigating the association between antenatal ART and perinatal outcomes.
- **Population**: HIV-positive pregnant women receiving antenatal ART with known adverse perinatal outcomes.
- **Exposure**: The use of any ART regimens during the antenatal period for at least 30 days. Studies had to specify the complexity (monotherapy, dual therapy and HAART), class (PI and non PI: NRTI, NNRTI, INSTI) and timing of initiation (pre-conception and post-conception: first-trimester, second-trimester, third trimester) of ART regimen. ART complexity was defined by

the number of ARV drugs used in the regimen: one ARV, two ARVs or at least three ARVs for monotherapy, dual therapy or HAART respectively. ART class was defined by the most complex ARV drug used in the regimen: 1) boosted PI, 2) non-boosted PI, 3) NNRTI, 4) INSTI and 5) NRTI or NtRTI. For HAART, the regimen class was defined by a third ARV drug used in the regimen (e.g. boosted PI); and the other two ARV drugs were considered as a "backbone" (e.g. NRTIs). Timing of ART initiation was defined by the start of ART medication: 1) pre-conception – before conception; 2) post-conception – after conception (first ART initiated during pregnancy), including first-trimester (<14 weeks'), second-trimester (14–28 weeks') and third-trimester (>28 weeks' gestation) initiation.

- **Comparator**: 1) HIV-negative pregnant women, 2) HIV-positive pregnant women without antenatal ART, or with antenatal ART for <30 days, 3) HIV-positive pregnant women receiving antenatal ART different from the exposure group in terms of ART complexity, class and timing of initiation.
- **Outcome**: The primary outcomes of interest included: 1) PTB ($<37^{+0}$ weeks' gestation), 2) VPTB ($<32^{+0}$ weeks' gestation), 3) sPTB (PTB after spontaneous initiation of labour), 4) sVPTB (VPTB after spontaneous initiation of labour), 5) LBW (BW <2500g), 6) VLBW (BW <1500g), 7) term LBW ($\geq 37^{+0}$ weeks' gestation and BW <2500g), 8) preterm LBW ($<37^{+0}$ weeks' gestation and BW <2500g), 9) SGA (BW for GA $<10^{th}$ centile) and 10) VSGA (BW for GA $<3^{rd}$ centile) based on reference charts used by study sites, 11) miscarriage (spontaneous expulsion of a fetus $<24^{+0}$ weeks' gestation), 12) stillbirth (third trimester delivery of an infant without any signs of life with BW ≥1000g or

gestational age $\geq 24^{+0}$ weeks or body length ≥35cm, 13) NND (death of an infant in the first 28 days of life). The secondary outcome of interest included MTCT defined as the results of the first newborn-HIV test indicating *in utero* or intrapartum transmission of HIV. The outcome of MTCT was analysed if one of the primary outcomes of interest was also reported by studies.

Studies were excluded if they had the following characteristics:

- **Study design**: Letters or comments to the editor, opinion pieces or case reports.
- **Population**: 1) Ambiguous eligibility criteria were used in participant recruitment, 2) HIV-positive pregnant women with co-existing diseases (e.g. tuberculosis), which were imbalanced between exposure and comparator groups included in the studies.
- **Exposure**: 1) ART was administered as a single-dose ART at delivery, or for duration of <30 days, 2) participants were exposed to additional medications (e.g. anti-tuberculosis drugs) during pregnancy, which were imbalanced between exposure and comparator groups.
- **Comparator**: Inappropriate comparators were used.
- **Outcome**: Adverse perinatal outcomes of interest were not defined or defined differently from those specified in the study protocol (Appendix 3.1).

Two independent reviewers identified duplicate articles by assessing the uniqueness of the study population of each article. If two or more articles reported the same cohort population, adverse perinatal outcomes of interest or ART comparisons; the one with the most recent and complete information was

included, while the others were excluded. If two or more articles reported the same cohort population but each article had different adverse perinatal outcomes of interest and/or ART comparisons, all these articles were included. Any ambiguities or discrepancies in the study selection process were resolved by discussion with the third reviewer until consensus was achieved.

3.3.2.2 Data extraction

For each eligible study, the first reviewers (CS, MK and ZB) extracted data for publication and study details, participant characteristics, exposures and outcomes (unadjusted and adjusted associations) using a pre-formulated data extraction tool in Microsoft Excel™ (Microsoft, Washington, USA). This was checked by the second reviewer (WS), and any discrepancies between the reviewers were resolved through discussion with the third reviewer (JH) until consensus was achieved. Authors were contacted for additional information, as necessary.

3.3.3 Methodological quality

The assessment of methodological quality was conducted for each eligible study by the first reviewers (CS, MK and ZB) and checked by the second reviewer (WS) using adapted versions of the Newcastle-Ottawa Scale used by Wedi et al. [365], as provided in Appendix 3.4 for the cohort and Appendix 3.5 for case-control studies. Any disagreements between the reviewers were resolved through discussion with the third reviewer (JH) until consensus was achieved. For cohort studies, the assessment was conducted using nine criteria that were grouped into three domains (Table 3.1 and Appendix 3.4): 1) selection of exposed and unexposed participants (maximum 4 points); 2) comparability of exposed and

unexposed participants, and whether adjustment for specific confounders was performed (maximum 2 points); 3) assessment of adverse perinatal outcomes of interest (maximum 3 points). Studies were classified into three levels: good, average and poor; as presented in Table 3.2. Case-control studies were assessed in a similar manner with minor modifications to take into account the study design (Table 3.1, Table 3.2 and Appendix 3.5).

Table 3.1. Adapted Newcastle-Ottawa quality assessment scale (Wedi et al. [365]).

Cohort studies
1. Selection of participants included in the study (maximum 4 points): • Representativeness of the exposed cohort? • Selection of the unexposed cohort? • Ascertainment of exposure? • Demonstration that outcome of interest was not present at the start of the study? **2. Comparability of exposed and unexposed participants (maximum 2 points):** • Did the study control for any of the following factors: body mass index, smoking, parity and maternal age? • Did the study control for any of the following additional factors: prior history of adverse perinatal outcome, maternal hypertension, anaemia, illicit drug or alcohol use during pregnancy? **3. Outcome (maximum 3 points):** • Is the assessment of the outcome valid? • Was gestational age accurately assessed? • Adequacy of follow-up of cohorts?
Case-control studies
1. Selection of cases and controls, and determination of gestational age (maximum 5 points): • Definition of cases (same as systematic review protocol)? • Representativeness of cases? • Selection of controls? • Definition of controls (same as systematic review protocol)? • Was gestational age accurately assessed in cases and controls? **2. Comparability of cases and controls (maximum 2 points):** • Did the study control for any of the following factors: body mass index, smoking, parity and maternal age.

- Did the study control for any of the following additional factors: prior history of adverse perinatal outcome, maternal hypertension, anaemia, illicit drug or alcohol use during pregnancy?

3. Assessment of the exposure (maximum 3 points):

- Is the assessment of exposure valid?
- Same method used of ascertainment for cases and controls?
- Non-response rate?

Table 3.2. Classification of studies according to the adapted Newcastle-Ottawa quality assessment scale (Wedi et al. [365]).

Quality	Study design	
	Cohort	**Case-control**
Good	9 points – all requirements met.	10 points – all requirements met.
Average	3 points in "selection" and 3 points in "outcomes" domains.	4 points in "selection" and 3 points in "exposure" domains.
	≥2 points in "selection" and "outcome" domains, and ≥1 points in "comparability" domains.	≥3 points in "selection" and ≥2 points in "exposure" domains, and ≥1 points in "comparability" domain.
Poor	<2 points in "selection" and/or "outcome" domains.	<3 points in "selection" and/or <2 points in "exposure" domains.
	2 points in "selection" and "outcome" domains, but no points in "comparability" domain.	3 points in "selection" and 2 points in "exposure" domains, but no points in "comparability" domain.

3.3.4 Data synthesis

Odds ratio (OR) and corresponding 95% confidence interval (CI) were used as a measure of associations between antenatal ART use and selected perinatal outcomes. For unadjusted associations, binary perinatal-outcomes data were extracted from all eligible studies (irrespective of their quality) and recorded in 2x2 tables in order to generate an unadjusted OR and 95% CI. For adjusted associations, adjusted effect estimates [OR or risk ratio (RR), and 95% CI] reported by individual studies were extracted. For studies which reported adjusted

RRs as a measure of association, the adjusted RR values were transformed into ORs using a formula proposed by Zhang et al. [384,386]. A meta-analysis was conducted when at least two studies reported the same perinatal outcomes and ART comparisons. A random-effects model was used to calculate a weighted summary effect estimate and 95% CI for the associations between antenatal ART use and adverse perinatal outcomes [384,387]. The I^2 statistic was used to quantify the percentage of variation in the effect estimate attributable to clinical or methodological heterogeneity, as opposed to sampling error [384,388]. The I^2 values <25% indicated none, 25-49% low, 50-74% moderate and ≥75% high heterogeneity [388]. For each outcome of interest, all summary effect estimates and 95% CIs were presented on forest plots.

Pre-specified sub-group analyses by study design (retrospective versus prospective) and World Bank country income status (low and middle-income versus high-income country) were conducted to assess the influence of these covariates on the associations between antenatal ART use and each adverse perinatal outcome. In order to determine the robustness of the meta-analysis results, when relevant, sensitivity analyses were performed to explore whether ART complexity, ART class, or timing of ART initiation influenced the observed summary effect estimates. For example, in the meta-analysis assessing the risk of PTB in women initiating ART pre-conception versus women initiating ART post-conception, sensitivity analyses according to ART class were performed by restricting the analysis to women on PI-based ART only and to women on non PI-based ART only. Thus, it could be determined whether the effect of pre-conception initiation on PTB risk was influenced by ART class. Exploration of

publication bias, or small-study effects was conducted graphically using contour-enhanced funnel plots [389,390] and statistically using the Harbord regression-based test [391,392] in each pairwise meta-analysis with a minimum of 10 studies.

All statistical analyses were conducted using STATA™ version 15.1 (StataCorp, Texas, USA). This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [393].

3.4 Results

3.4.1 Literature search

The literature searches identified 52,211 citations after removing duplicates. After review of the titles and abstracts, 2,427 studies were assessed for eligibility criteria, and 79 studies were included in final meta-analysis: 49 retrospective and 30 prospective cohorts (Figure 3.1).

3.4.2 Description of included studies

The 79 cohorts reported data on 234,464 participants recruited during the period of 1984–2017, and were published between 1998 and 2018 (Table 3.3). Of the 79 cohorts, 27 (34.2%) were conducted in sub-Saharan Africa, 27 (34.2%) Europe, 21 (26.6%) the Americas, 3 (3.8%) Asia; and the remaining one (1.2%) in multi-regions: sub-Saharan Africa (Ethiopia), Europe (Russia, UK), the Americas (Argentina, Brazil, Canada, Puerto Rico, USA) and Asia and Pacific (Australia, Israel) (Table 3.3). More than half (n=128,340; 54.7%) of the 234,464 participants assessed, were from sub-Saharan Africa.

The median number of participants included in individual studies was 760 (range: 19 to 44,370). Mean maternal age varied among studies from 25.5 to 34.2 years (Table 3.3), as did maternal HIV stages (Appendix 3.6: Table 3.1). Other detailed characteristics of the studies included in the present systematic review are provided in Appendix 3.6: Table 3.1.

"HAART versus non HAART" was the most frequently investigated ART comparison (n=33) followed by "PI versus non PI-based ART" (n=30), "combination therapy versus monotherapy" (n=27), "HAART versus monotherapy" (n=26), "pre-conception versus post-conception initiation of ART" (n=26), "treated HIV-positive versus untreated HIV-positive" (n=25), "treated HIV-positive versus HIV-negative" (n=17), "first-trimester versus after first-trimester initiation of ART" (n=12), "dual therapy versus monotherapy" (n=10) and "HAART versus dual therapy" (n=8). PTB (n=62) was the most frequently reported adverse perinatal outcome followed by LBW (n=39), SGA (n=25), VPTB (n=14), MTCT (n=13), VLBW (n=10), sPTB (n=6), VSGA (n=6), stillbirth (n=6) and NND (n=4) (Table 3.3).

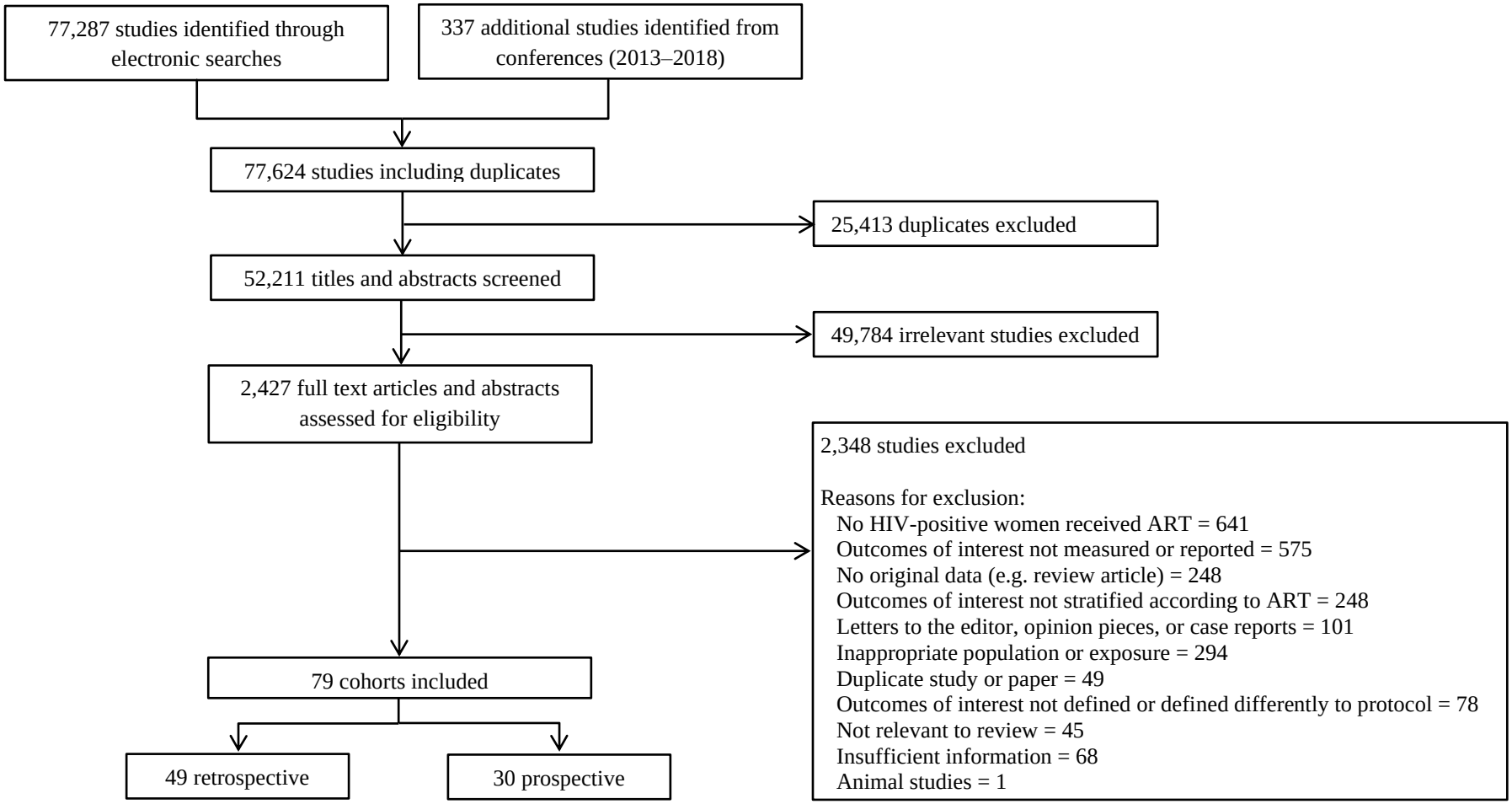


Figure 3.1. Flow diagram of study selection process. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Table 3.3. Overall characteristics of studies included in the systematic review.

Characteristics	**Number of studies (N=79) n (%)[§]**
Number of participants	234,464
<100	9 (11.4)
100–<500	23 (29.1)
500–<2000	25 (31.7)
≥2000	22 (27.8)
Recruitment period	1984–2017
Year of publication	1998–2018
<2004	6 (7.6)
2004–2009	11 (13.9)
2010–2015	38 (48.1)
≥2016	24 (30.4)
Geographical region	
Sub-Saharan Africa	27 (34.2)
Europe	27 (34.2)
The Americas	21 (26.6)
Asia	3 (3.8)
Multi-regions	1 (1.2)
World Bank country–income status	
Low and middle income	33 (41.8)
High income	45 (56.9)
Mixed	1 (1.3)
Study site	
Single-centre	28 (35.4)
Multiple-centres	38 (48.1)
Not reported	13 (16.5)
Twin pregnancies included in the analysis	18 (22.8)
Mean[ǂ] maternal age (years), mean (range)	28.9 (25.5, 34.2)
25–28	30 (38)
29–32	19 (24)
33–36	4 (5.1)
Not reported	26 (32.9)

Table 3.3. Overall characteristics of studies included in the systematic review (*continued from previous page*).

Characteristics	Number of studies (N=79) n (%)[§]
Potential risk factors/comorbidities reported by the studies	
Low CD4 count <200 cells/mm^3	25 (31.7)
Smoking	25 (31.7)
Alcohol consumption	14 (17.7)
Illicit drug use	33 (41.8)
Anaemia	15 (19)
Pregnancy-induced hypertension	3 (3.8)
Adverse perinatal outcomes examined	
Preterm birth	62 (78.5)
Spontaneous preterm birth	6 (7.6)
Very preterm birth	14 (17.7)
Low birth weight	39 (49.4)
Very low birth weigh	10 (12.7)
Small for gestational age	25 (31.6)
Very small for gestational age	6 (7.6)
Stillbirth	6 (7.6)
Neonatal death	4 (5.1)
Mother-to-child transmission	13 (16.5)
ART comparisons	
Treated HIV-positive versus HIV-negative	17 (21.5)
Treated HIV-positive versus untreated HIV-positive	25 (31.6)
Combination therapy versus monotherapy	27 (34.2)
Dual therapy versus monotherapy	10 (12.7)
HAART versus monotherapy	26 (32.9)
HAART versus dual therapy	8 (10.1)
HAART versus non HAART	33 (41.8)
PI versus non PI-based ART	30 (38)
Pre-conception versus post-conception initiation of ART	26 (32.9)
First-trimester versus after first-trimester initiation of ART	12 (15.2)

[§] Percentages were calculated from the total number of cohorts included in the systematic review (N=79).
[l] Average of reported medians or means for 53 cohorts.
Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; PI, protease inhibitor.

3.4.2.1 Methods to estimate gestational age

Information on methods of gestational-age estimation was provided by almost two-thirds of included cohorts (n=51; 64.6%). Of these, 41 used a combination of methods (mixed methods) as presented in Table 3.4; 10 used a single method including early or late ultrasound (n=3), LNMP (n=4), SFH (n=1) and neonatal assessments using Finnström score (n=1) and Capuro method (n=1).

Table 3.4. Combination of methods (mixed methods) to estimate gestational age in studies included in the systematic review.

Methods to estimate gestational age	Number of studies
Early[§] or late[l] ultrasound, LNMP	4
Early ultrasound, LNMP	6
Late ultrasound, LNMP	1
Ultrasound (unspecified), LNMP, SFH, neonatal assessment (unspecified)	3
Ultrasound (unspecified), LNMP, SFH	7
Ultrasound (unspecified), LNMP, neonatal assessment (unspecified)	3
Ultrasound (unspecified), LNMP, clinical assessment (unspecified)	4
Ultrasound (unspecified), LNMP	9
Ultrasound (unspecified), clinical assessment (unspecified)	1
LNMP, SFH	2
LNMP, neonatal assessment (unspecified)	1

[§] Ultrasound in the first trimester.
[l] Ultrasound after first trimester.
Abbreviations: LNMP, last normal menstrual period; SFH, symphysis-fundal height.

3.4.2.2 Controlling for confounding factors

From the 79 included cohorts, 42 controlled for confounding factors (40 through multivariable analysis and two matching) in the association between antenatal ART and adverse perinatal outcomes (Table 3.5).

Table 3.5. Controlling for confounding factors in studies included in the systematic review.

Study	Controlling for confounding factors	
	Matching	Multivariable analysis
Sub-Saharan Africa		
Adam et al. 2016 [394]	–	–
Chaudhury et al. 2018 [395]	–	–
Chen et al. 2012 [15]	–	Marital status, education, smoking, alcohol use, history of adverse perinatal outcomes, hypertension in pregnancy, anaemia, history of TB, CD4 count
Chetty et al. 2018 [13]	–	Maternal age, year of delivery, type of antenatal clinic, ART duration, CD4 count
Dryden-Peterson et al. 2011 [396]	–	–
Ekouevi et al. 2008 [397]	–	Maternal age, education, BMI, having partner, having income activity, HIV stage, CD4 count
Ezechi et al. 2012 [398]	–	–
Joseph et al. 2011 [374]	–	–
Li et al. 2015 [376]	–	Year of delivery, facility level, short stature, MUAC, Hb and ALT levels, history of TB, CD4 count
Malaba et al. 2017 [29]	–	Maternal age, height, parity, previous PTB, CD4 count, viral load
Marazzi et al. 2011 [368]	–	–
Moodley et al. 2016 [28]	–	Maternal age, mode of delivery, pregnancy term, CD4 count
Nlend et al. 2016 [16]	–	Maternal age, parity, CD4 count
Olagbuji et al. 2010 [399]	–	–
Powis et al. 2016 [67]	–	–
Ramokolo et al. 2017 [14]	–	Maternal age, race, education, SES, food insecurity, parity, number of antenatal visits, syphilis serology, TB, newborn sex
Rempis et al. 2017 [400]	–	–
Sebitloane et al. 2017 [356]	–	–
Shapiro et al. 2010 [154]	–	–
Silverman et al. 2010 [401]	–	–
The Kesho Bora Study Group et al. 2010 [17]	–	–

Table 3.5. Controlling for confounding factors in studies included in the systematic review (*continued from previous page*).

Study	Controlling for confounding factors	
	Matching	**Multivariable analysis**
Sub-Saharan Africa		
van der Merwe et al. 2011 [30]	–	Maternal age, hypertension, CD4 count
Wilkinson et al. 2015 [402]	–	–
Zash et al. 2016 [403]	–	Maternal age, education, employment, anaemia, hypertension, CD4 count
Zash et al. 2017 [96]	–	Maternal age, education, gravidity
Zash et al. 2018 [404]	–	Maternal age, education, parity
Zash et al. IAS 2017 [405]	–	Maternal age, education, gravidity
Europe		
Boer et al. 2006 [406]	Maternal age, race, parity, delivery date	–
ECS et al. 2003 [383]	–	Maternal age, illicit drug use, CD4 count
Favarato et al. 2018 [407]	–	Maternal age, country of origin, history of injectable drug use, year of delivery, parity, CD4 count
Favarato et al. IAS 2017 [408]	–	Maternal age, country of origin, history of injectable drug use, year of delivery, parity, late ANC start, CD4 count, newborn sex
Feiterna-Sperling et al. 2007 [409]	–	–
Grignolo et al. 2017 [375]	–	Smoking, illicit drug use, mode of HIV transmission
Grosch-Woerner et al. 2008 [378]	–	–
Hernandez et al. 2016 [410]	Maternal age, parity	–
Kowalska et al. 2003 [23]	–	–
Lopez et al. 2012 [411]	–	History of PTB, nulliparity
Lopez et al. 2015 [412]	–	–
Mandelbrot et al. 1998 [413]	–	–
Mandelbrot et al. 2001 [414]	–	Mode of delivery, HIV stage, history of ART use
Mandelbrot et al. 2015 [152]	–	–
Montgomer-Taylor et al. 2015 [415]	–	–
Oomeer et al. 2015 [416]	–	–
Rudin et al. 2011 [370]	–	Maternal age, race, drugs use, smoking, CD4 count, VL
Samuel et al. 2014 [153]	–	–

Table 3.5. Controlling for confounding factors in studies included in the systematic review (*continued from previous page*).

Study	Controlling for confounding factors	
	Matching	**Multivariable analysis**
Europe		
Short et al. 2014 [18]	–	Maternal age, ethnicity, parity, baseline CD4 count, VL
Sibiude et al. 2012 (main) [20]	–	Maternal age, country of origin, drug use, CD4 count
Sibiude et al. 2012 (sub 1) [20]	–	Maternal age, marital status, smoking, drug use, BMI, assisted conception, GA at first visit, HCV co-infection, CD4 count, VL
Sibiude et al. 2012 (sub 2) [20]	–	–
Snijdewind et al. 2018 [417]	–	Parity, region of origin
Thorne et al. IAS 2017 [418]	–	–
Townsend et al. 2007 (NSHPC) [381]	–	Maternal age, race, injecting drug use, repeated pregnancies, HIV clinical status, CD4 count
Townsend et al. 2010 (ECS) [19]	–	Race, region of birth, injecting drug use, HIV clinical status, year of delivery, study site
Townsend et al. 2010 (NSHPC) [19]	–	Race, region of birth, injecting drug use, HIV clinical status, year of delivery, study site
The Americas		
Aaron et al. 2012 [419]	–	–
Cooper et al. 2002 [420]	–	–
Cotter et al. 2006 [25]	–	Race, smoking, alcohol and drug use, year of delivery, history of PTB, STD, HIV stage, CD4 count, ART duration, pre-pregnancy ART
Duryea et al. 2015 [366]	–	Maternal age, race, duration of HIV diagnosis, CD4 count, VL
Einstein et al. 2004 [421]	–	–
Gagnon et al. 2016 [422]	–	Ethnicity, history of PTB and medical history
Haeri et al. 2009 [423]	–	Smoking, cocaine use
Hofer et al. 2016 [367]	–	–
Kakkar et al. 2015 [22]	–	Maternal age, race, parity, HCV status, CD4 count
Machado et al. 2009 [24]	–	Parity, hypertension, STD, viral load
Mounce et al. 2017 [424]	–	–
Papp et al. 2015 [425]	–	–

Table 3.5. Controlling for confounding factors in studies included in the systematic review (*continued from previous page*).

Study	Controlling for confounding factors	
	Matching	**Multivariable analysis**
The Americas		
Patel et al. 2010 [380]	–	Smoking, alcohol and drug use, gravidity, GA at enrolment, history of PTB, gestational diabetes and hypertension, bleeding, HIV stage, CD4 count, VL, ART duration
Phiri et al. 2015 [369]	–	Smoking, alcohol use, year of birth, HIV-related maternal illness during pregnancy
Ransom et al. 2013 [426]	–	–
Schulte et al. 2007 [371]	–	Race, drug use, HIV stage, infant HIV status
Simonds et al. 1998 [427]	–	–
Szyld et al. 2006 [382]	–	BMI, hypertension, diabetes, mode of delivery
Townsend et al. 2010 (PSD) [19]	–	Race, drug use, year of delivery, clinical HIV status, study site
Watts et al. 2013 [372]	–	Race, income, CD4 count
Williams et al. 2013 [428]	–	–
Asia		
Ai-jie et al. 2013 [373]	–	–
Chakornbandit et al. 2015 [21]	–	–
Darak et al. 2013 [429]	–	Maternal age, CD4 count
Multi-regions		
Vannappagari et al. IAS 2017 [430]	–	–

Abbreviations: ALT, alanine aminotransferase; ANC, antenatal care; ART, antiretroviral therapy; BMI, body mass index; ECS, European Collaborative Study; GA, gestational age; Hb, haemoglobin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IAS, International AIDS Society Conference on HIV Science; MUAC, mid-upper arm circumference; NSHPC, National Study of HIV in Pregnancy and Childhood; PSD, Pediatric Spectrum of HIV Disease; PTB, preterm birth; SES, socioeconomic status; STD, sexually transmitted disease; TB, tuberculosis; VL, viral load.

3.4.2.3 Assessment of methodological quality

Of the 79 cohorts included in the systematic review, 41 (51.9%) were assessed as poor and 38 (48.1%) as average quality studies (Table 3.6). None of cohorts were assessed as a good quality study because most did not use a first-trimester ultrasound to estimate gestational age (Table 3.4) and were unable to control for pre-specified confounders (Table 3.5).

Table 3.6. Quality assessment scores of studies included in the systematic review according to the adapted Newcastle-Ottawa quality assessment guidelines.

Study	**Quality assessment**			
	Selection (maximum 4 points)	**Comparability** (maximum 2 points)	**Outcome** (maximum 3 points)	**Overall quality assessment** (good/average/poor)
Sub-Saharan Africa				
Adam et al. 2016 [394]	⋆⋆⋆	⋆⋆	⋆	Poor
Chaudhury et al. 2018 [395]	⋆⋆⋆⋆	-	⋆⋆	Poor
Chen et al. 2012 [15]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Chetty et al. 2018 [13]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Dryden-Peterson et al. 2011 [396]	⋆⋆	⋆	⋆	Poor
Ekouevi et al. 2008 [397]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Ezechi et al. 2012 [398]	⋆⋆	⋆	⋆⋆	Average
Joseph et al. 2011 [374]	⋆⋆	⋆⋆	⋆⋆	Average
Li et al. 2015 [376]	⋆⋆⋆⋆	⋆⋆	⋆	Poor
Malaba et al. 2017 [29]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Marazzi et al. 2011 [368]	⋆⋆	⋆	⋆⋆	Average
Moodley et al. 2016 [28]	⋆⋆	⋆	⋆⋆	Average
Nlend et al. 2016 [16]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Olagbuji et al. 2010 [399]	⋆⋆	⋆⋆	-	Poor
Powis et al. 2016 [67]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Ramokolo et al. 2017 [14]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Rempis et al. 2017 [400]	⋆⋆	⋆⋆	⋆	Poor
Sebitloane et al. 2017 [356]	⋆⋆	-	⋆⋆	Poor
Shapiro et al. 2010 [154]	⋆⋆⋆⋆	-	⋆⋆⋆	Average
Silverman et al. 2010 [401]	-	-	⋆	Poor
The Kesho Bora Study Group et al. 2010 [17]	⋆⋆⋆	-	⋆	Poor
van der Merwe et al. 2011 [30]	⋆	⋆⋆	⋆⋆	Poor
Wilkinson et al. 2015 [402]	⋆⋆⋆⋆	-	⋆⋆	Poor
Zash et al. 2016 [403]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Zash et al. 2017 [96]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Zash et al. 2018 [404]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Zash et al. IAS 2017 [405]	⋆⋆⋆	⋆⋆	⋆	Poor
Europe				
Boer et al. 2006 [406]	-	⋆⋆	⋆⋆	Poor
ECS et al. 2003 [383]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Favarato et al. 2018 [407]	⋆⋆⋆	⋆⋆	⋆⋆	Average

Table 3.6. Quality assessment scores of studies included in the systematic review according to the adapted Newcastle-Ottawa quality assessment guidelines (*continued from previous page*).

Study	**Quality assessment**			
	Selection (maximum 4 points)	**Comparability** (maximum 2 points)	**Outcome** (maximum 3 points)	**Overall quality assessment** (good/average/poor)
Europe				
Favarato et al. IAS 2017 [408]	⋆⋆⋆	⋆⋆	⋆	Poor
Feiterna-Sperling et al. 2007 [409]	⋆⋆⋆	-	⋆⋆	Poor
Grignolo et al. 2017 [375]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Grosch-Woerner et al. 2008 [378]	⋆⋆⋆⋆	-	⋆⋆	Poor
Hernandez et al. 2016 [410]	⋆⋆⋆	⋆	⋆⋆	Average
Kowalska et al. 2003 [23]	⋆⋆⋆	-	⋆	Poor
Lopez et al. 2012 [411]	⋆	⋆⋆	⋆	Poor
Lopez et al. 2015 [412]	⋆⋆	-	⋆⋆	Poor
Mandelbrot et al. 1998 [413]	⋆⋆⋆	-	⋆	Poor
Mandelbrot et al. 2001 [414]	⋆⋆	-	⋆	Poor
Mandelbrot et al. 2015 [152]	⋆⋆⋆	-	⋆	Poor
Montgomer-Taylor et al. 2015 [415]	⋆⋆	-	⋆⋆	Poor
Oomeer et al. 2015 [416]	⋆⋆	-	⋆	Poor
Rudin et al. 2011 [370]	⋆⋆⋆⋆	⋆⋆	-	Poor
Samuel et al. 2014 [153]	⋆⋆	-	⋆⋆	Poor
Short et al. 2014 [18]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Sibiude et al. 2012 (main) [20]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Sibiude et al. 2012 (sub 1) [20]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Sibiude et al. 2012 (sub 2) [20]	⋆⋆	-	⋆⋆	Poor
Snijdewind et al. 2018 [417]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Thorne et al. IAS 2017 [418]	⋆⋆⋆	-	⋆	Poor
Townsend et al. 2007 (NSHPC) [381]	⋆⋆⋆	⋆⋆	⋆	Poor
Townsend et al. 2010 (ECS) [19]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Townsend et al. 2010 (NSHPC) [19]	⋆⋆⋆	⋆	-	Poor

Table 3.6. Quality assessment scores of studies included in the systematic review according to the adapted Newcastle-Ottawa quality assessment guidelines (*continued from previous page*).

Study	**Quality assessment**			
	Selection (maximum 4 points)	**Comparability** (maximum 2 points)	**Outcome** (maximum 3 points)	**Overall quality assessment** (good/average/poor)
The Americas				
Aaron et al. 2012 [419]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Cooper et al. 2002 [420]	⋆⋆⋆⋆	-	⋆	Poor
Cotter et al. 2006 [25]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Duryea et al. 2015 [366]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Einstein et al. 2004 [421]	⋆⋆	-	⋆	Poor
Gagnon et al. 2016 [422]	⋆⋆	⋆	⋆⋆	Average
Haeri et al. 2009 [423]	⋆⋆	⋆⋆	⋆⋆	Average
Hofer et al. 2016 [367]	⋆⋆	-	⋆⋆	Poor
Kakkar et al. 2015 [22]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Machado et al. 2009 [24]	⋆⋆⋆	⋆⋆	⋆	Poor
Mounce et al. 2017 [424]	⋆⋆	-	⋆⋆	Poor
Papp et al. 2015 [425]	⋆⋆⋆	-	⋆	Poor
Patel et al. 2010 [380]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Phiri et al. 2015 [369]	⋆⋆	⋆⋆	⋆⋆	Average
Ransom et al. 2013 [426]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Schulte et al. 2007 [371]	⋆⋆⋆	⋆	⋆⋆	Average
Simonds et al. 1998 [427]	⋆⋆⋆	-	⋆⋆	Poor
Szyld et al. 2006 [382]	⋆⋆⋆⋆	⋆⋆	⋆⋆	Average
Townsend et al. 2010 (PSD) [19]	⋆⋆⋆	⋆	⋆⋆	Average
Watts et al. 2013 [372]	⋆⋆	⋆	⋆⋆	Average
Williams et al. 2013 [428]	⋆⋆⋆	-	⋆⋆	Poor
Asia				
Ai-jie et al. 2013 [373]	⋆⋆	-	⋆⋆	Poor
Chakornbandit et al. 2015 [21]	⋆⋆⋆	-	⋆⋆	Poor
Darak et al. 2013 [429]	⋆⋆⋆	⋆⋆	⋆⋆	Average
Multi-regions				
Vannappagari et al. IAS 2017 [430]	⋆⋆⋆	-	⋆	Poor

Abbreviations: ECS, European Collaborative Study; IAS, International AIDS Society Conference on HIV Science; NSHPC, National Study of HIV in Pregnancy and Childhood; PSD, Pediatric Spectrum of HIV Disease.

3.4.3 Effect of maternal HIV/ART on perinatal outcomes

The first aim was assessed by conducting pairwise meta-analyses comparing the risk of adverse perinatal outcomes in treated HIV-positive versus HIV-negative pregnant women. The exposure group was HIV-positive pregnant women receiving any ART irrespective of its complexity, class and timing of initiation; the comparator group was HIV-negative pregnant women.

3.4.3.1 Effect of maternal HIV/ART on gestational age at delivery

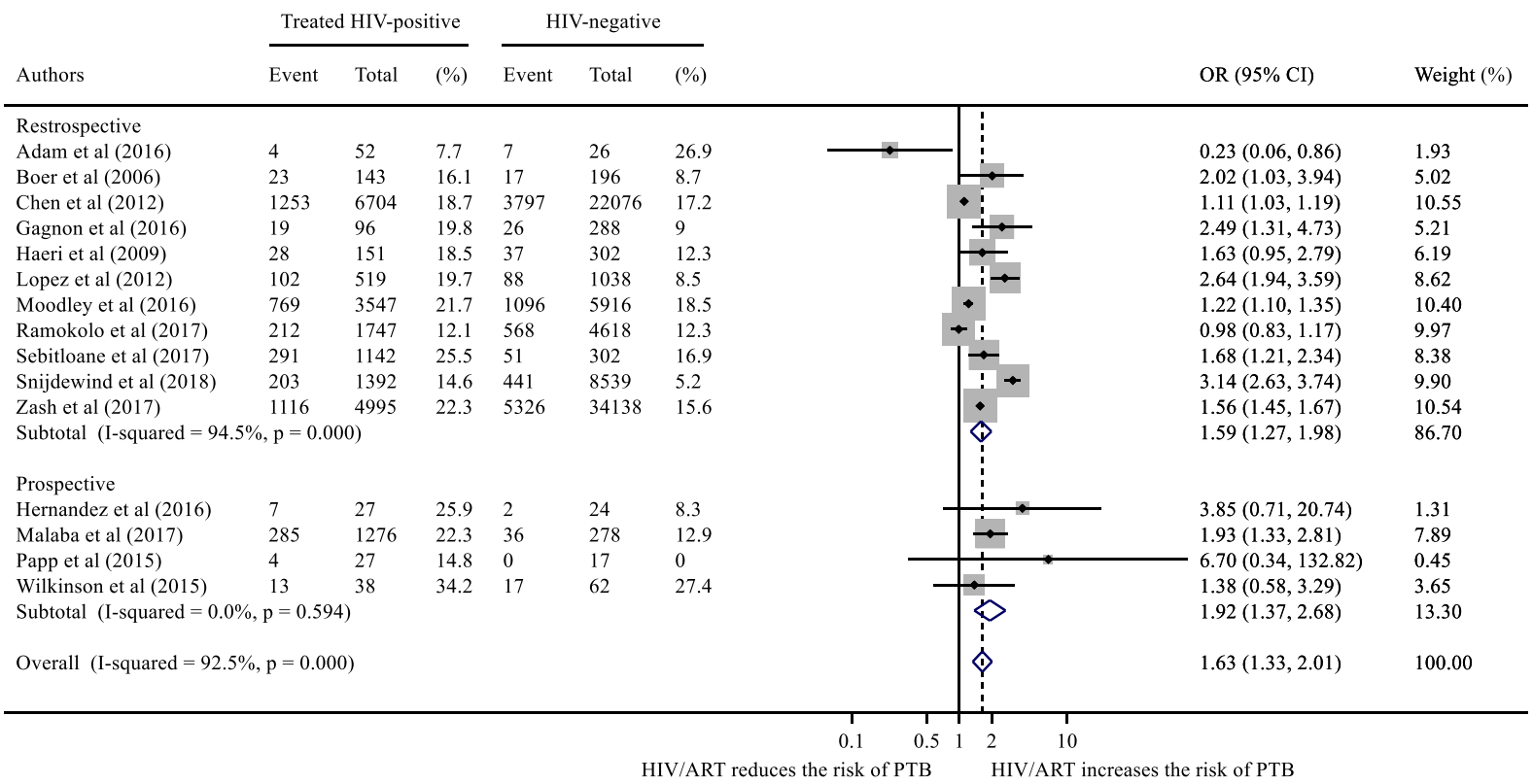
3.4.3.1.1 Preterm birth (PTB)

PTB was reported by 15 cohorts (11 retrospective and four prospective) including 153,905 women; eight cohorts were conducted in LMICs and seven in high-income countries (Figure 3.2). The pooled data showed an association between treated maternal HIV infection and an increased risk of PTB compared with HIV negative women (pooled OR: 1.63, 95% CI: 1.33, 2.01) (Figure 3.2). Between-study heterogeneity was high (I^2 = 92.5%), suggesting that around 92% of the variation in effect estimate was attributed to heterogeneity between studies rather than chance (Figure 3.2). In sub-group analysis by cohort design, both retrospective (pooled OR: 1.59, 95% CI: 1.27, 1.98) and prospective cohorts (pooled OR: 1.92, 95% CI: 1.37, 2.68) showed an association between treated maternal HIV infection and an increased risk of PTB compared with HIV-negative women; a high degree of heterogeneity was observed in the retrospective (I^2 = 94.5%) but not prospective cohorts (I^2 = 0%) (Figure 3.2A). In sub-group analysis by country-income status, both LMIC (pooled OR: 1.29, 95% CI: 1.08, 1.54) and high-income country (pooled OR: 2.68, 95% CI: 2.23, 3.23) showed an association between treated maternal HIV infection and an increased risk of PTB

compared with HIV-negative women; a high degree of heterogeneity was observed in LMIC (I^2 = 89.7%), but not high-income country (I^2 = 16.4%) (Figure 3.2B).

Figure 3.3 shows a contour-enhanced funnel plot for the 15 cohorts comparing the risk of PTB in treated HIV-positive versus HIV-negative pregnant women. The funnel is centred not at the model estimate, but at 0 – the value under the null hypothesis of no effect. The solid red vertical line corresponds to the estimated summary log(OR); solid black circles indicate the 15 studies; solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10, respectively. The region between the two green lines in the middle corresponds to *P* values >0.10; the region between the green and blue lines corresponds to *P* values between 0.10 and 0.05; the region between the blue and purple lines corresponds to *P* values between 0.05 and 0.01; and the region outside the funnel corresponds to *P* values <0.01. These contours help determine whether the regions where studies (solid black circles) are potentially missing are of low statistical significance. If studies are missing in regions of low statistical significance, the asymmetry is possibly due to publication bias. The contour-enhanced funnel plot in Figure 3.3 seems symmetric suggesting no evidence of publication bias; Harbord's test showed a *P* value of 0.231 suggesting no evidence of small-study effects.

A


Treated HIV-positive
HIV-negative
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Restrospective
Adam et al (2016) 4 52 7.7 7 26 26.9 0.23 (0.06, 0.86) 1.93
Boer et al (2006) 23 143 16.1 17 196 8.7 2.02 (1.03, 3.94) 5.02
Chen et al (2012) 1253 6704 18.7 3797 22076 17.2 1.11 (1.03, 1.19) 10.55
Gagnon et al (2016) 19 96 19.8 26 288 9 2.49 (1.31, 4.73) 5.21
Haeri et al (2009) 28 151 18.5 37 302 12.3 1.63 (0.95, 2.79) 6.19
Lopez et al (2012) 102 519 19.7 88 1038 8.5 2.64 (1.94, 3.59) 8.62
Moodley et al (2016) 769 3547 21.7 1096 5916 18.5 1.22 (1.10, 1.35) 10.40
Ramokolo et al (2017) 212 1747 12.1 568 4618 12.3 0.98 (0.83, 1.17) 9.97
Sebitloane et al (2017) 291 1142 25.5 51 302 16.9 1.68 (1.21, 2.34) 8.38
Snijdewind et al (2018) 203 1392 14.6 441 8539 5.2 3.14 (2.63, 3.74) 9.90
Zash et al (2017) 1116 4995 22.3 5326 34138 15.6 1.56 (1.45, 1.67) 10.54
Subtotal (I-squared = 94.5%, p = 0.000) 1.59 (1.27, 1.98) 86.70
Prospective
Hernandez et al (2016) 7 27 25.9 2 24 8.3 3.85 (0.71, 20.74) 1.31
Malaba et al (2017) 285 1276 22.3 36 278 12.9 1.93 (1.33, 2.81) 7.89
Papp et al (2015) 4 27 14.8 0 17 0 6.70 (0.34, 132.82) 0.45
Wilkinson et al (2015) 13 38 34.2 17 62 27.4 1.38 (0.58, 3.29) 3.65
Subtotal (I-squared = 0.0%, p = 0.594) 1.92 (1.37, 2.68) 13.30
Overall (I-squared = 92.5%, p = 0.000) 1.63 (1.33, 2.01) 100.00
0.1
0.5
1
2
10
HIV/ART reduces the risk of PTB
HIV/ART increases the risk of PTB

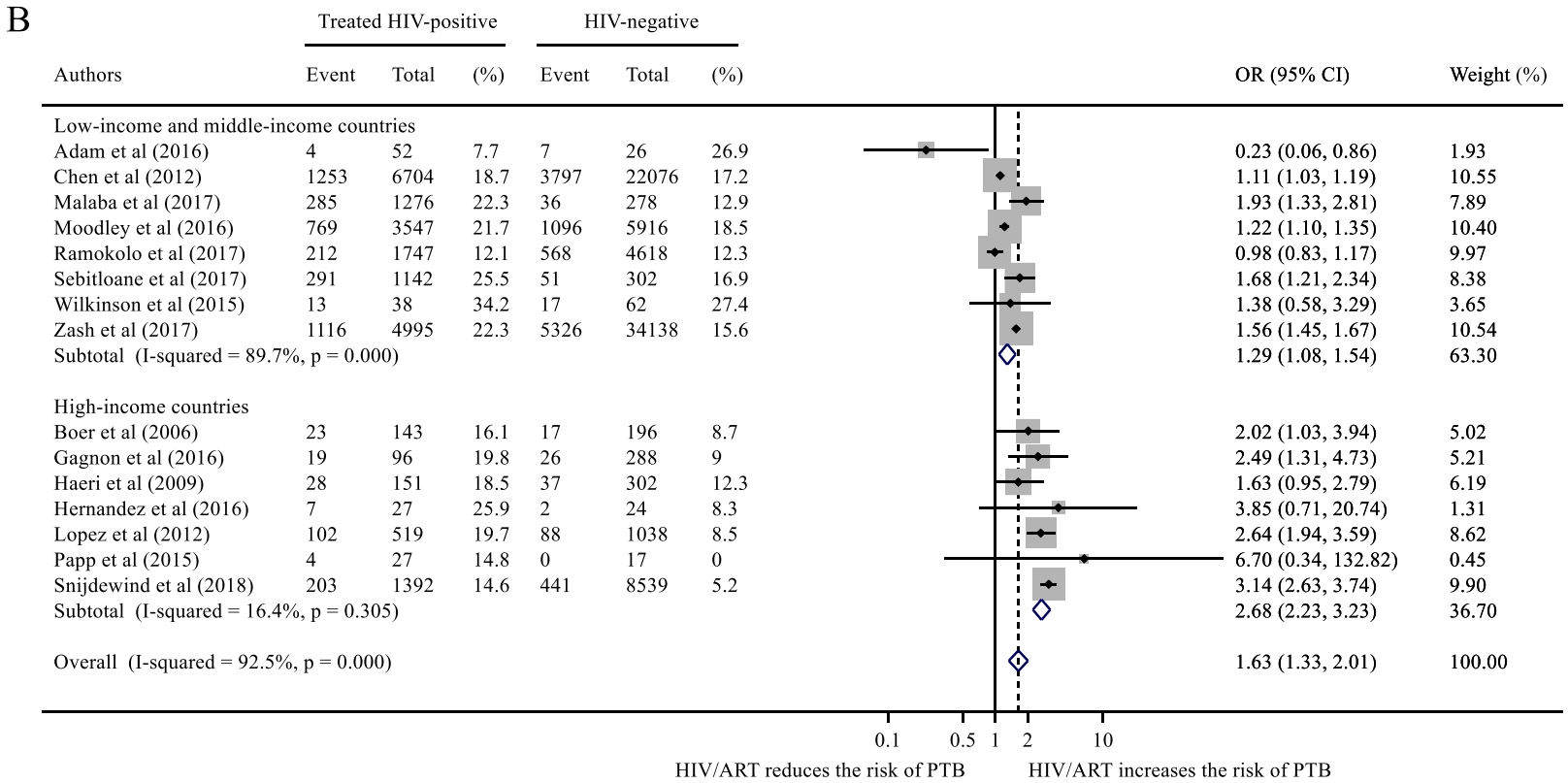


Figure 3.2. Forest plots of risk of preterm birth in treated HIV-positive versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

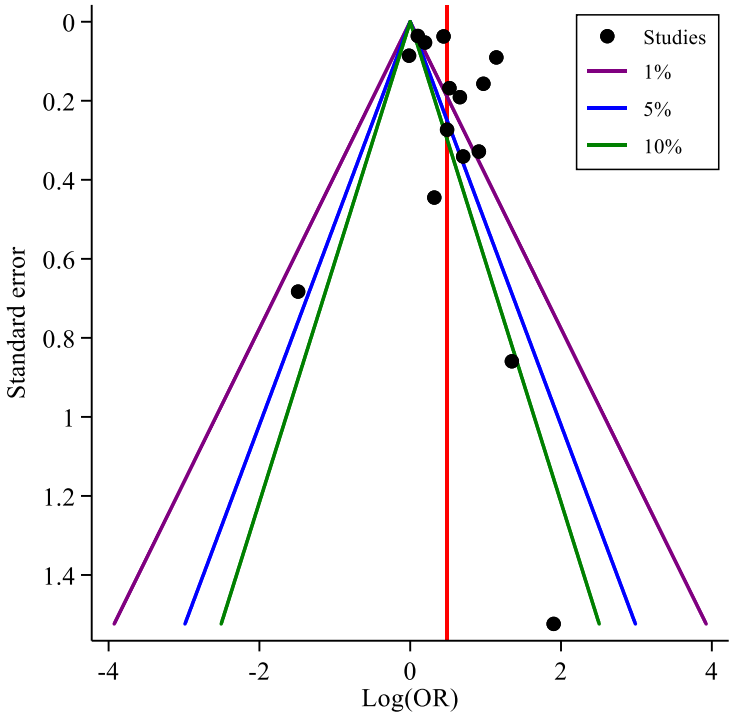


Figure 3.3. Contour-enhanced funnel plot of the 15 cohorts comparing the risk of preterm birth in treated HIV-positive versus HIV-negative pregnant women using unadjusted data. Solid black circles correspond to the 15 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 15 cohorts, 12 specified ART complexity: five used both non HAART and HAART, seven used HAART only (Appendix 3.7: Figure 3.1 and Figure 3.2). HIV-positive women receiving HAART had a higher risk of PTB than HIV-negative women (pooled OR: 1.77, 95% CI: 1.45, 2.15) (Appendix 3.7: Figure 3.2). However, there was no difference in PTB risk between HIV-positive women receiving non HAART and HIV-negative women (pooled OR: 1.18, 95% CI: 0.89, 1.57) (Appendix 3.7: Figure 3.1). Eight cohorts specified ART class: five used both non PI and PI-based regimens, three used non PI-based regimens only (Appendix 3.7: Figure 3.3). HIV-positive women treated with non PI (pooled OR: 1.52, 95% CI: 1.23, 1.89) (Appendix 3.7: Figure 3.3A) or PI-based regimens

(pooled OR: 2.30, 95% CI: 1.81, 2.92) (Appendix 3.7: Figure 3.3B) had a higher risk of PTB than HIV-negative women. Eight cohorts specified timing of ART initiation: five included women who initiated ART both pre-conception and post-conception, one pre-conception and two post-conception only (Appendix 3.7: Figure 3.4). HIV-positive women who initiated ART pre-conception (pooled OR: 1.93, 95% CI: 1.51, 2.46) (Appendix 3.7: Figure 3.4A), but not post-conception (pooled OR: 1.27, 95% CI: 0.93, 1.74) (Appendix 3.7: Figure 3.4B), showed a higher risk of PTB than HIV-negative women.

Of the 15 cohorts, four were included in the meta-analysis of adjusted effect estimates and showed that treated HIV-positive women had an increased risk of PTB compared with HIV-negative women (pooled adjusted OR: 2.25, 95% CI: 1.79, 2.81); no heterogeneity was observed (I^2 = 0%) (Figure 3.4). Sub-group analyses by cohort design, and by country-income status were not performed because, of the four cohorts, only one was prospective and conducted in an LMIC [29].

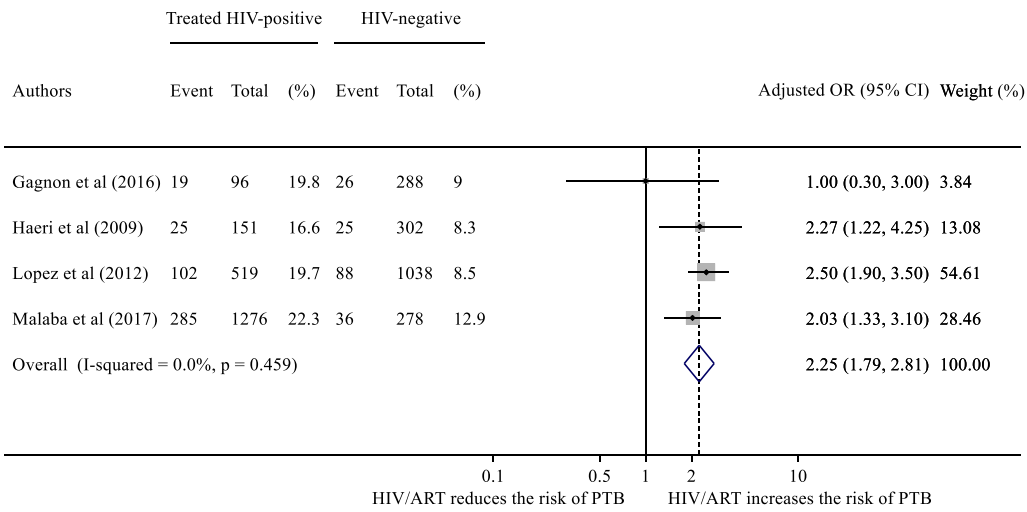


Figure 3.4. Forest plot of risk of preterm birth in treated HIV-positive versus HIV-negative pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

3.4.3.1.2 Spontaneous preterm birth (sPTB)

The pooled data of three cohorts including 2,054 women showed an association between treated maternal HIV infection and an increased risk of sPTB compared with HIV negative women (pooled OR: 2.27, 95% CI: 1.68, 3.06) (Figure 3.5A). The finding remained when the meta-analysis was performed using the adjusted effect estimates of two cohorts (pooled adjusted OR: 2.14, 95% CI: 1.58, 2.90) (Figure 3.5B).

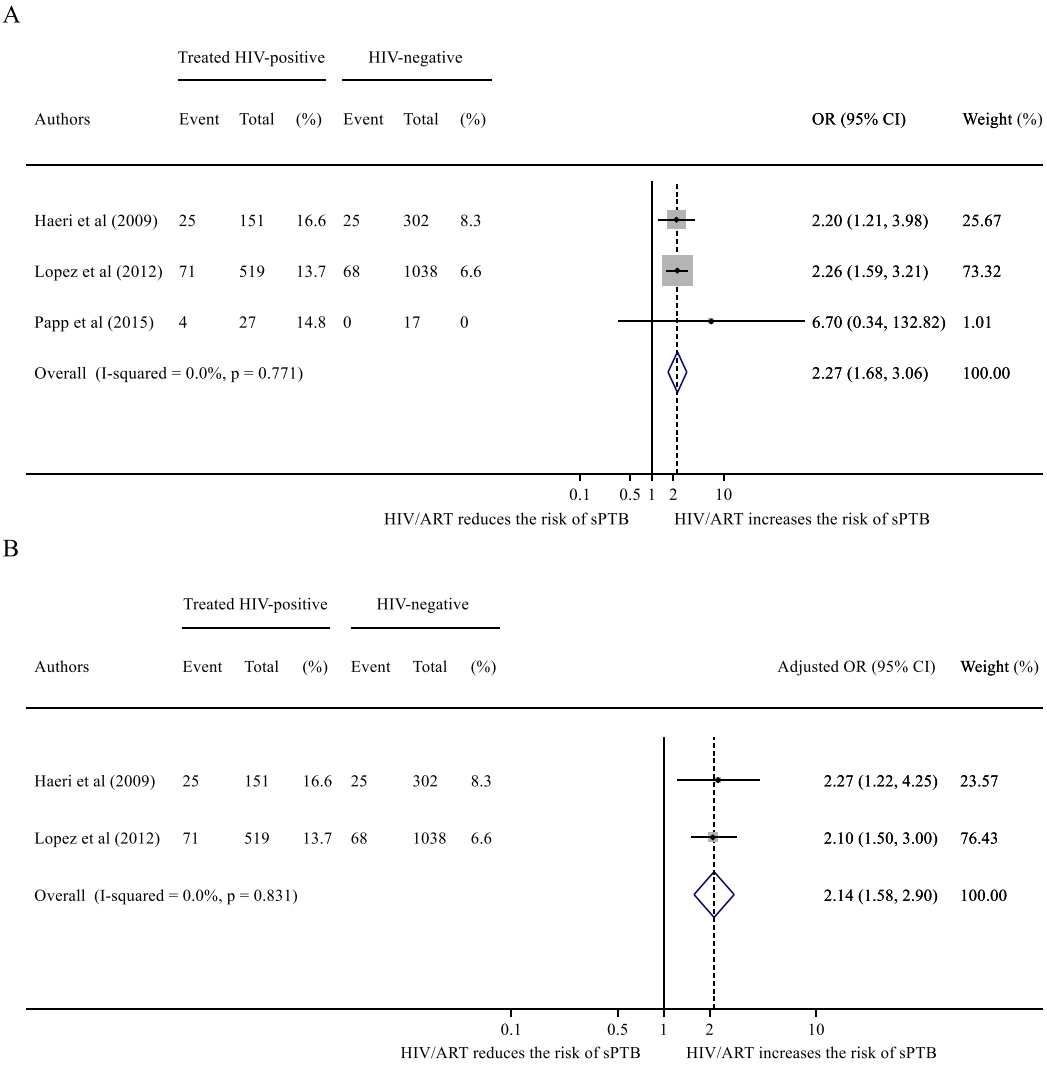


Figure 3.5. Forest plots of risk of spontaneous preterm birth in treated HIV-positive versus HIV-negative pregnant women using unadjusted (A) and adjusted effect estimates (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; sPTB, spontaneous preterm birth.

3.4.3.1.3 Very preterm birth (VPTB)

The pooled data of four cohorts (three retrospective and one prospective) including 52,175 women, revealed an association between treated maternal HIV infection and an increased risk of VPTB compared with HIV-negative women (pooled OR: 2.59, 95% CI: 1.15, 5.80), with a high degree of heterogeneity (I^2 =

91.4%) (Figure 3.6). Sub-group analysis by country-income status showed an association between treated maternal HIV infection and an increased risk of VPTB in high-income country (pooled OR: 3.69, 95% CI: 1.93, 7.04), but not LMIC (pooled OR: 1.43, 95% CI: 0.96, 2.14) (Figure 3.6). Sub-group analysis by cohort design was not performed because, of the four cohorts, only one was prospective [29]. Of the four cohorts, one reported an adjusted effect estimate indicating a higher risk of VPTB in treated HIV-positive than HIV-negative women (adjusted OR: 2.40, 95% CI: 1.23, 4.70) [411].

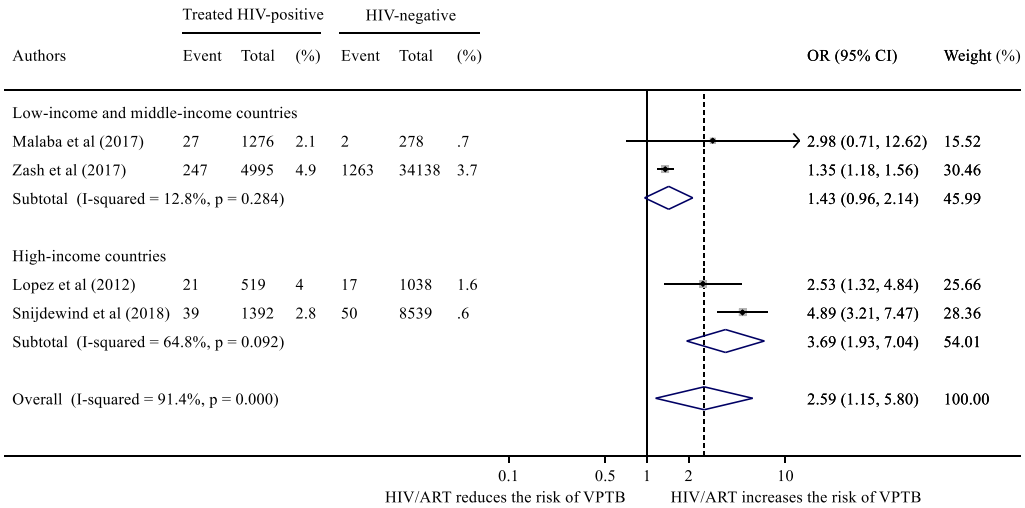


Figure 3.6. Forest plot of risk of very preterm birth in treated HIV-positive versus HIV-negative pregnant women using unadjusted data, by country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VPTB, very preterm birth.

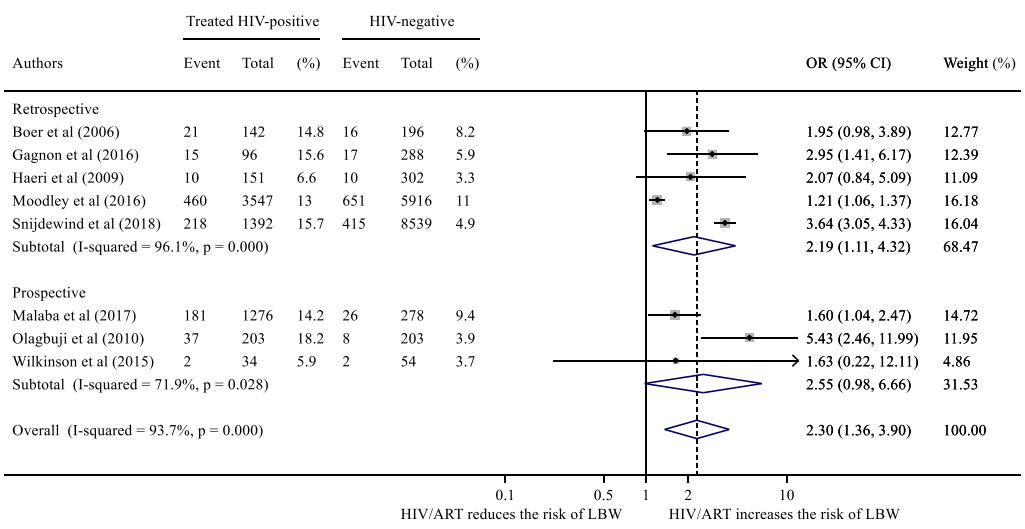
3.4.3.2 Effect of maternal HIV/ART on birth weight

3.4.3.2.1 Low birth weight (LBW)

LBW was reported by eight cohorts (five retrospective and three prospective) including 22,617 women; four cohorts were conducted in LMICs and four in

high-income countries (Figure 3.7). Treated maternal HIV infection was associated with an increased risk of LBW compared with HIV-negative women (pooled OR: 2.30, 95% CI: 1.36, 3.90), with a high degree of heterogeneity (I^2 = 93.7%) (Figure 3.7). In sub-group analysis by cohort design, the association was observed in retrospective (pooled OR: 2.19, 95% CI: 1.11, 4.32), but not prospective cohorts (pooled OR: 2.55, 95% CI: 0.98, 6.66) (Figure 3.7A). In sub-group analysis by country-income status, both LMIC (pooled OR: 1.90, 95% CI: 1.05, 3.43) and high-income country (pooled OR: 2.99, 95% CI: 2.17, 4.13) showed an association between treated maternal HIV infection and an increased risk of LBW. A high degree of heterogeneity (I^2 = 79.7%) was observed in LMIC, but low heterogeneity (I^2 = 31.6%) in high-income country (Figure 3.7B).

A



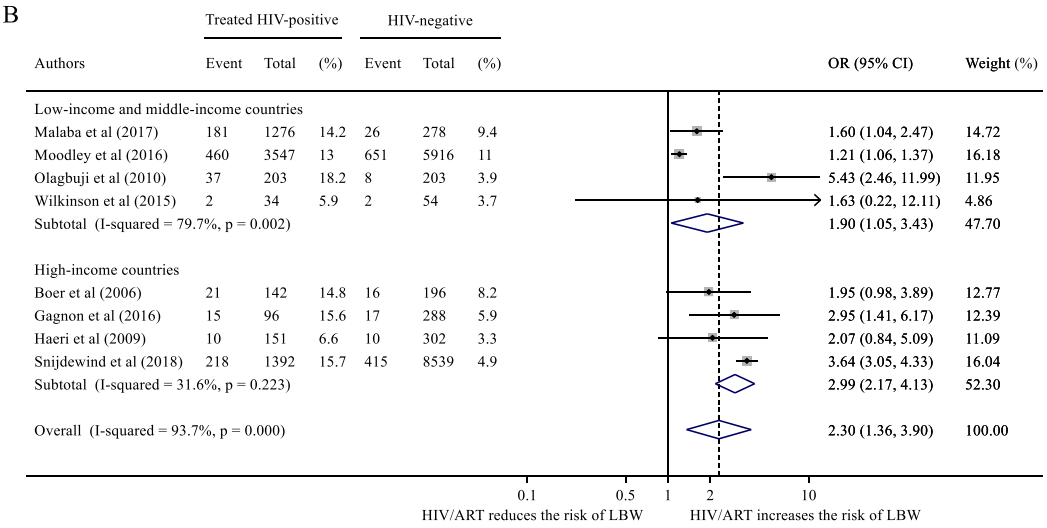


Figure 3.7. Forest plots of risk of low birth weight in treated HIV-positive versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

Of the eight cohorts, six specified ART complexity: one used both non HAART and HAART, and five used HAART only (Appendix 3.7: Figure 3.5 and Figure 3.6). HIV-positive women on HAART showed an increased risk of LBW compared with HIV-negative women (pooled OR: 2.30, 95% CI: 1.33, 3.97) (Appendix 3.7: Figure 3.6). However, no difference in LBW risk was observed between HIV-positive women on non HAART and HIV-negative women (one study, OR: 0.89, 95% CI: 0.71, 1.12) (Appendix 3.7: Figure 3.5). Four cohorts specified ART class: two used both non PI and PI-based regimens, and two used non PI-based regimens only (Appendix 3.7: Figure 3.7). HIV-positive women on non PI (pooled OR: 2.48, 95% CI: 1.14, 5.39) (Appendix 3.7: Figure 3.7A) or PI-based regimens (pooled OR: 3.33, 95% CI: 2.72, 4.07) (Appendix 3.7: Figure 3.7B) showed an increased risk of LBW compared with HIV-negative women.

Four cohorts specified timing of ART initiation: two included HIV-positive women initiating ART both pre-conception and post-conception, and two post-conception only (Appendix 3.7: Figure 3.8). HIV-positive women initiating ART pre-conception (pooled OR: 2.78, 95% CI: 1.03, 7.52) (Appendix 3.7: Figure 3.8A) or post-conception (pooled OR: 2.25, 95% CI: 1.18, 4.31) (Appendix 3.7: Figure 3.8B) had a higher risk of LBW than HIV-negative women.

The meta-analysis of adjusted effect estimates of two cohorts showed no difference in LBW risk between treated HIV-positive and HIV-negative pregnant women (pooled adjusted OR: 1.47, 95% CI: 0.93, 2.33) (Figure 3.8).

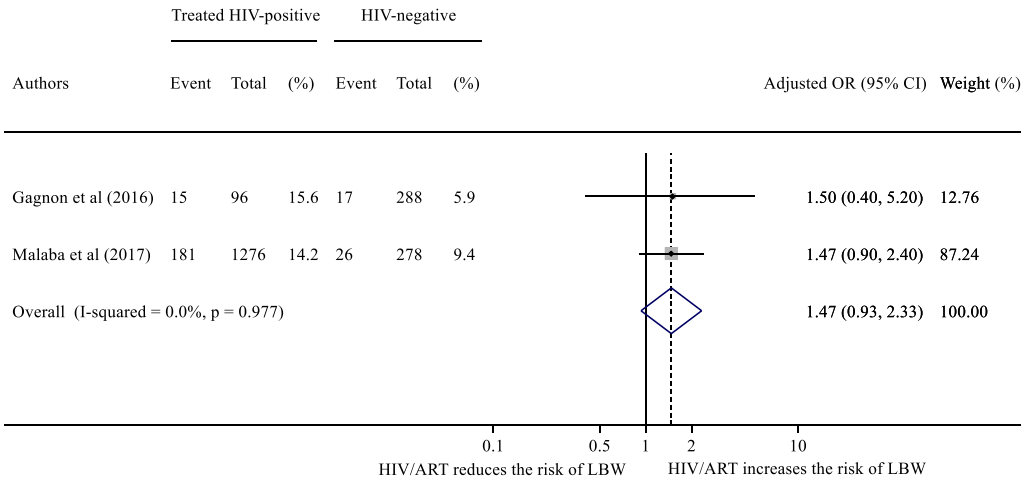


Figure 3.8. Forest plot of risk of low birth weight in treated HIV-positive versus HIV-negative pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

3.4.3.2.2 Very low birth weight (VLBW)

The meta-analysis of three cohorts (including 11,823 women) in which all HIV-positive women were on HAART, showed no association between treated

maternal HIV infection and VLBW risk compared with HIV-negative women (pooled OR: 1.96, 95% CI: 0.42, 9.04) (Figure 3.9)

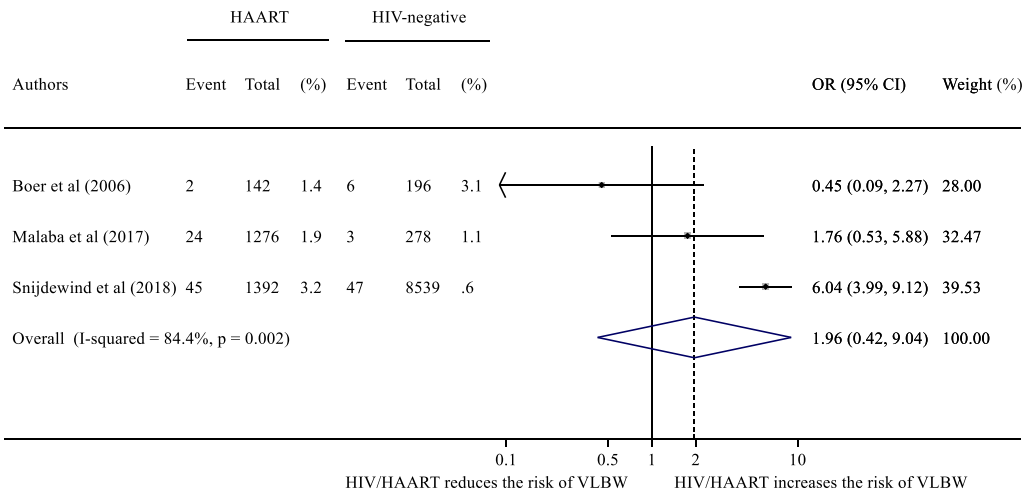


Figure 3.9. Forest plot of risk of very low birth weight in treated HIV-positive versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VLBW, very low birth weight.

Of the three cohorts, two specified ART class: both used non PI and PI-based HAART (Appendix 3.7: Figure 3.9A and Figure 3.9B). HIV-positive pregnant women receiving PI (pooled OR: 4.44, 95% CI: 2.70, 7.29) (Appendix 3.7: Figure 3.9B), but not non PI-based HAART (pooled OR: 4.57, 95% CI: 0.86, 24.35) (Appendix 3.7: Figure 3.9A), showed a higher risk of VLBW than HIV-negative women. Two cohorts specified timing of ART initiation: both included HIV-positive women with pre-conception and post-conception initiation (Appendix 3.7: Figure 3.10A and Figure 3.10B). HIV-positive women starting HAART post-conception (pooled OR: 3.34, 95% CI: 1.31, 8.49) (Appendix 3.7: Figure 3.10B),

but not pre-conception (pooled OR: 4.25, 95% CI: 0.86, 20.99) (Appendix 3.7: Figure 3.10A), showed a higher risk of VLBW than HIV-negative women.

3.4.3.3 Effect of maternal HIV/ART on gestational age and birth weight combined

3.4.3.3.1 Small for gestational age (SGA)

SGA was reported by nine cohorts (six retrospective and three prospective) including 61,412 women; four cohorts were conducted in LMICs and five in high-income countries (Figure 3.10). The pooled data of nine cohorts showed an association between treated maternal HIV infection and an increased risk of SGA compared with HIV-negative women (pooled OR: 2.45, 95% CI: 1.15, 5.21), with a high degree of heterogeneity (I^2 = 98.5%) (Figure 3.10). In sub-group analysis by cohort design, the association was observed in retrospective (pooled OR: 2.44, 95% CI: 1.01, 5.89), but not prospective cohorts (pooled OR: 3.22, 95% CI: 0.38, 27.06) (Figure 3.10A). Sub-group analysis by country-income status showed an association between treated maternal HIV infection and an increased risk of SGA in high-income country (pooled OR: 5.68, 95% CI: 1.54, 20.99), but not in LMIC (pooled OR: 1.18, 95% CI: 0.86, 1.62) (Figure 3.10B).

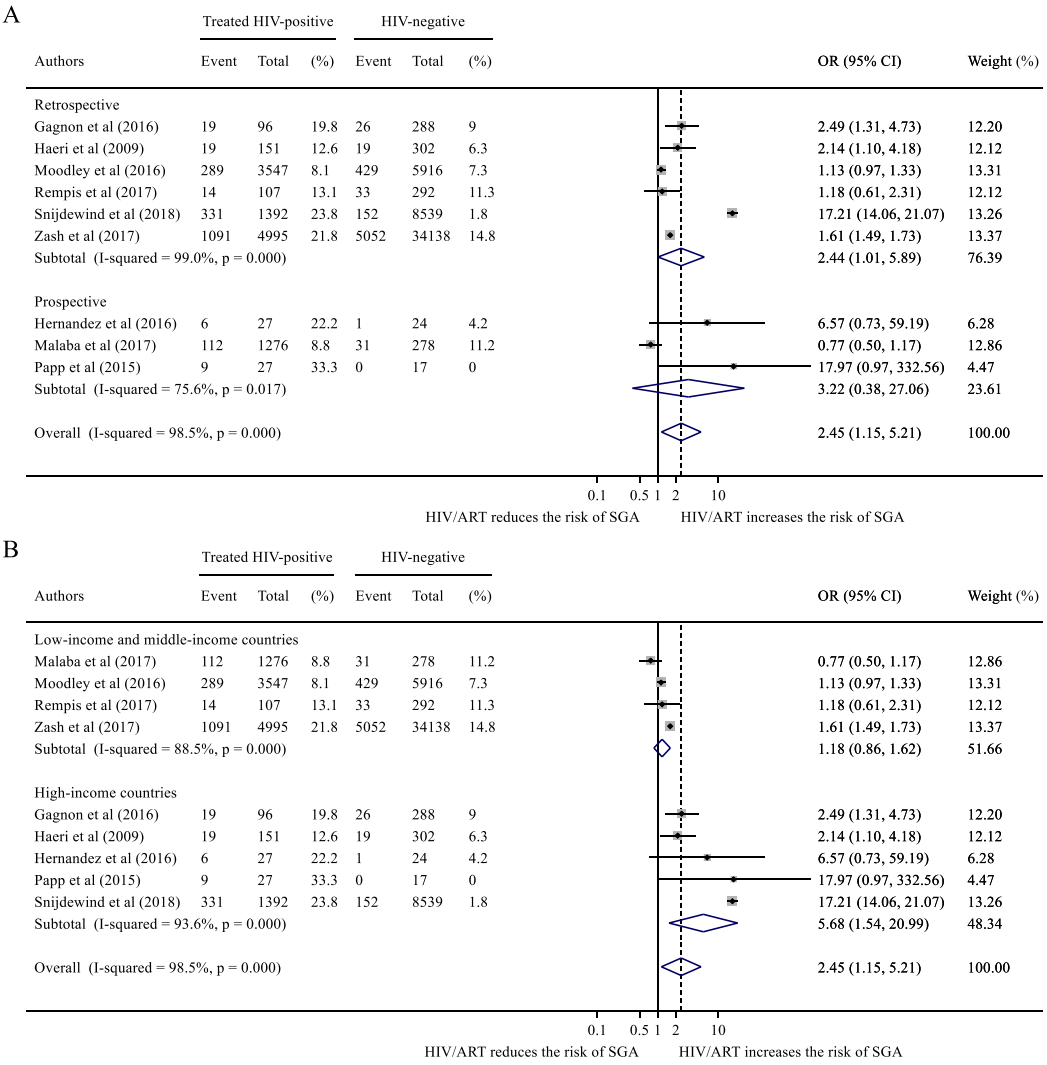


Figure 3.10. Forest plots of risk of small for gestational age in treated HIV-positive versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

Of the nine cohorts, eight specified ART complexity: one used both non HAART and HAART, and seven used HAART only (Appendix 3.7: Figure 3.11 and Figure 3.12). HIV-positive women treated with HAART (pooled OR: 2.44, 95% CI: 1.05, 5.65) (Appendix 3.7: Figure 3.12), but not non HAART (one study, OR: 1.04, 95% CI: 0.80, 1.34) (Appendix 3.7: Figure 3.11), showed a higher risk of

SGA than HIV-negative women. Five cohorts specified ART class: three used both non PI and PI-based regimens, and two used non PI-based regimens only (Appendix 3.7: Figure 3.13). HIV-positive women treated with non PI (pooled OR: 2.06, 95% CI: 0.91, 4.65) (Appendix 3.7: Figure 3.13A) or PI-based regimens (pooled OR: 3.25, 95% CI: 0.54, 19.72) (Appendix 3.7: Figure 3.13B) were not associated with SGA compared with HIV-negative women. Five cohorts specified timing of ART initiation: four included women initiating ART both pre-conception and post-conception, and one post-conception only (Appendix 3.7: Figure 3.14). HIV-positive women initiating ART pre-conception (pooled OR: 2.33, 95% CI: 0.48, 11.24) (Appendix 3.7: Figure 3.14A) or post-conception (pooled OR: 2.01, 95% CI: 0.82, 4.95) (Appendix 3.7: Figure 3.14B) were not associated with SGA compared with HIV-negative women.

The meta-analysis of adjusted effect estimates of three cohorts showed no difference in SGA risk between treated HIV-positive and HIV-negative pregnant women (pooled adjusted OR: 1.18, 95% CI: 0.76, 1.82) (Figure 3.11).

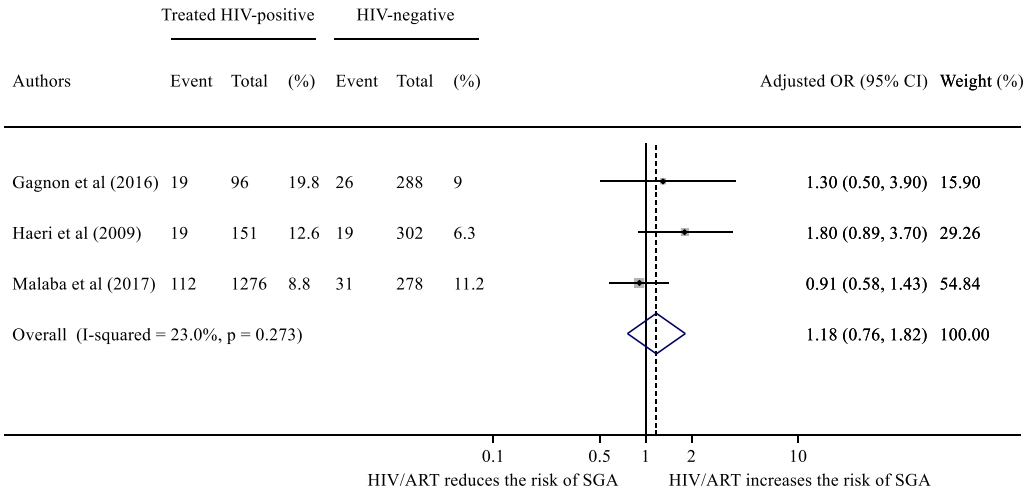


Figure 3.11. Forest plot of risk of small for gestational age in treated HIV-positive versus HIV-negative pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

3.4.3.3.2 Very small for gestational age (VSGA)

A retrospective cohort conducted in an LMIC, including 39,133 women, showed an association between treated maternal HIV infection and an increased risk of VSGA compared with HIV-negative women (OR: 1.90, 95% CI: 1.71, 2.11) [96].

3.4.3.4 Effect of maternal HIV/ART on fetal and neonatal mortality

A retrospective cohort conducted in an LMIC showed an association between treated maternal HIV infection and an increased risk of stillbirth (OR: 1.74, 95% CI: 1.48, 2.06), but not NND (OR: 1.17, 95% CI: 0.97, 1.41), compared with HIV-negative women [96].

3.4.3.5 Summary of meta-analysis results

The summary of meta-analysis results for the effect of maternal HIV/ART on perinatal outcomes is provided in Appendix 3.7: Tables 3.2 and 3.3.

3.4.4 Effect of maternal ART on perinatal outcomes

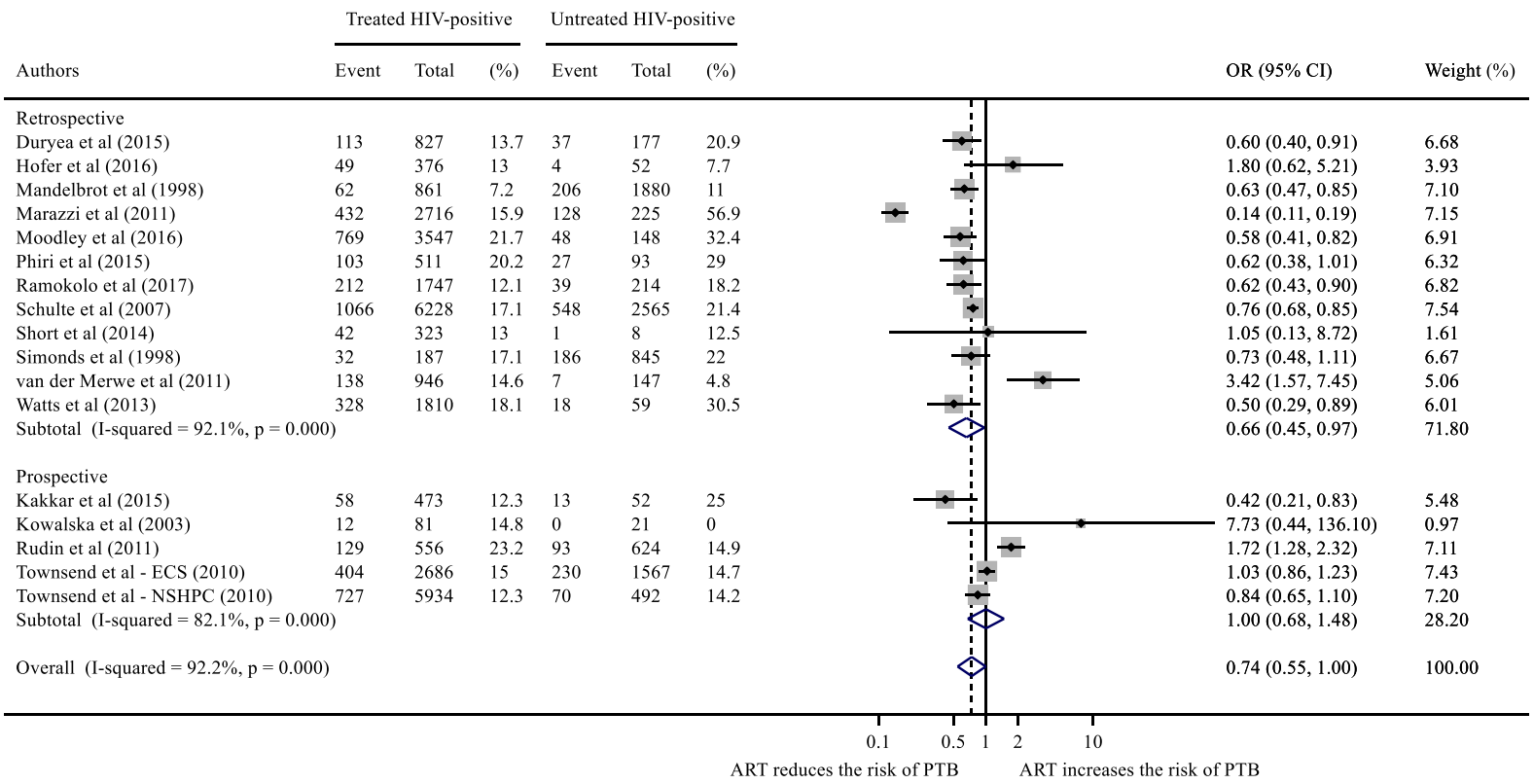
The second aim was investigated by conducting pairwise meta-analyses assessing the risk of adverse perinatal outcomes in treated HIV-positive versus untreated HIV-positive pregnant women. The exposure group was HIV-positive pregnant women receiving any ART regimens irrespective of ART complexity, class and timing of initiation; the comparator group was HIV-positive pregnant women receiving no ART.

3.4.4.1 Effect of maternal ART on gestational age at delivery

3.4.4.1.1 Preterm birth (PTB)

PTB was reported by 20 cohorts (12 retrospective and eight prospective) including 47,873 women; five cohorts were conducted in LMICs and 15 in high-income countries. Three prospective cohorts [381,383,420] conducted in high-income countries, including 8,895 women, were excluded from the meta-analysis due to the possibility of overlap with other studies [19,372]. The pooled unadjusted effect estimates of 17 cohorts showed an association between any ART and a decreased risk of PTB at borderline statistical significance (pooled OR: 0.74, 95% CI: 0.55, 1.00), with high degree of heterogeneity (I^2 = 92.2%) (Figure 3.12). In sub-group analysis by cohort design, an association between ART and a decreased risk of PTB was observed in retrospective (pooled OR: 0.66, 95% CI: 0.45, 0.97) but not prospective cohorts (pooled OR: 1.00, 95% CI: 0.68, 1.48) (Figure 3.12A). This association persisted in the meta-analysis of cohorts conducted in high-income countries (pooled OR: 0.79, 95% CI: 0.64, 0.97), but not in LMICs (pooled OR: 0.75, 95% CI: 0.28, 2.01) (Figure 3.12B).

A


Treated HIV-positive
Untreated HIV-positive
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Duryea et al (2015) 113 827 13.7 37 177 20.9 0.60 (0.40, 0.91) 6.68
Hofer et al (2016) 49 376 13 4 52 7.7 1.80 (0.62, 5.21) 3.93
Mandelbrot et al (1998) 62 861 7.2 206 1880 11 0.63 (0.47, 0.85) 7.10
Marazzi et al (2011) 432 2716 15.9 128 225 56.9 0.14 (0.11, 0.19) 7.15
Moodley et al (2016) 769 3547 21.7 48 148 32.4 0.58 (0.41, 0.82) 6.91
Phiri et al (2015) 103 511 20.2 27 93 29 0.62 (0.38, 1.01) 6.32
Ramokolo et al (2017) 212 1747 12.1 39 214 18.2 0.62 (0.43, 0.90) 6.82
Schulte et al (2007) 1066 6228 17.1 548 2565 21.4 0.76 (0.68, 0.85) 7.54
Short et al (2014) 42 323 13 1 8 12.5 1.05 (0.13, 8.72) 1.61
Simonds et al (1998) 32 187 17.1 186 845 22 0.73 (0.48, 1.11) 6.67
van der Merwe et al (2011) 138 946 14.6 7 147 4.8 3.42 (1.57, 7.45) 5.06
Watts et al (2013) 328 1810 18.1 18 59 30.5 0.50 (0.29, 0.89) 6.01
Subtotal (I-squared = 92.1%, p = 0.000) 0.66 (0.45, 0.97) 71.80
Prospective
Kakkar et al (2015) 58 473 12.3 13 52 25 0.42 (0.21, 0.83) 5.48
Kowalska et al (2003) 12 81 14.8 0 21 0 7.73 (0.44, 136.10) 0.97
Rudin et al (2011) 129 556 23.2 93 624 14.9 1.72 (1.28, 2.32) 7.11
Townsend et al - ECS (2010) 404 2686 15 230 1567 14.7 1.03 (0.86, 1.23) 7.43
Townsend et al - NSHPC (2010) 727 5934 12.3 70 492 14.2 0.84 (0.65, 1.10) 7.20
Subtotal (I-squared = 82.1%, p = 0.000) 1.00 (0.68, 1.48) 28.20
Overall (I-squared = 92.2%, p = 0.000) 0.74 (0.55, 1.00) 100.00
0.1
0.5
1
2
10
ART reduces the risk of PTB
ART increases the risk of PTB

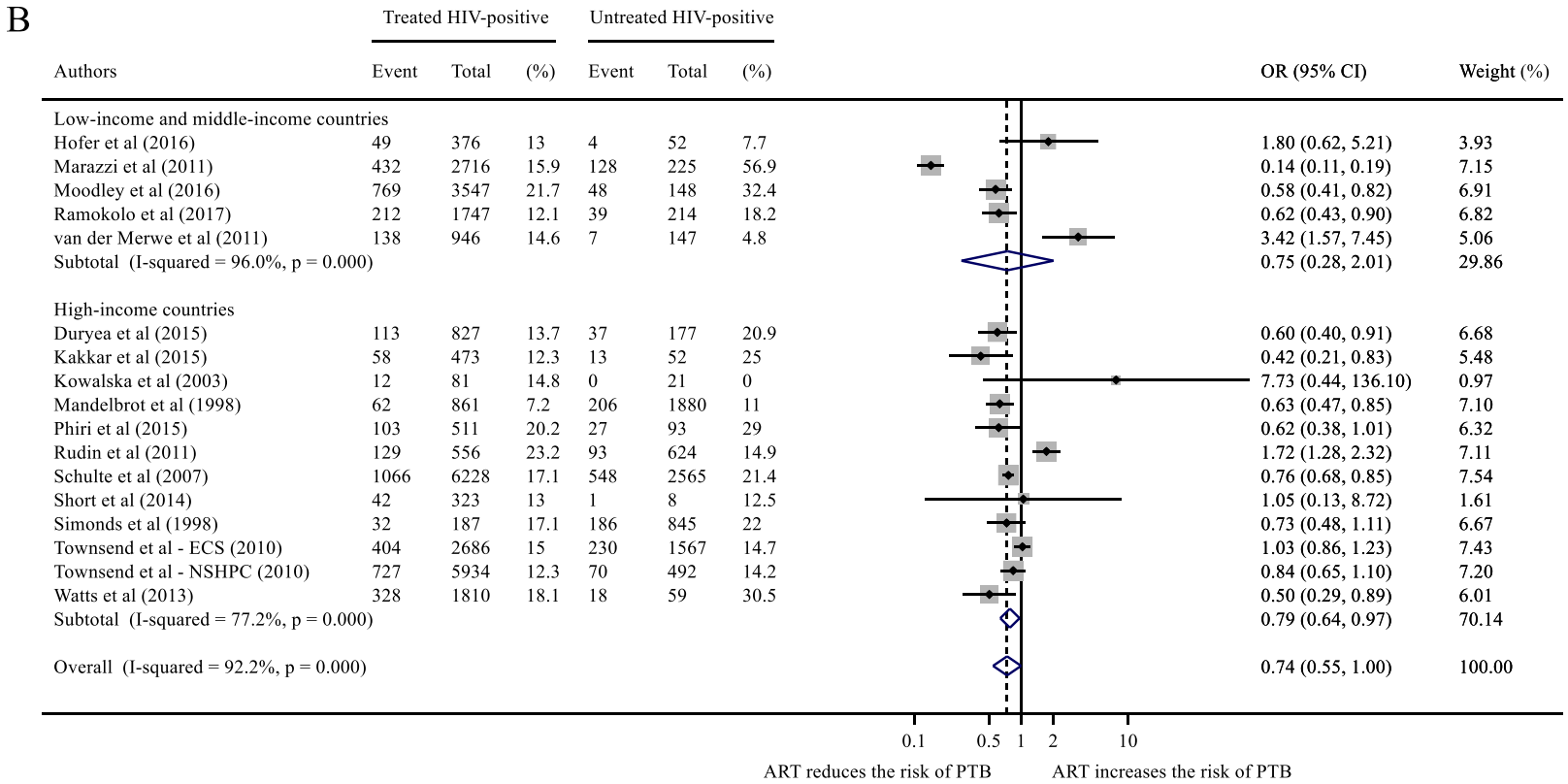


Figure 3.12. Forest plots of risk of preterm birth in treated versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

The contour-enhanced funnel plot in Figure 3.13 is rather symmetric indicating no evidence of publication bias; Harbord's test showed a *P* value of 0.741 indicating no evidence of small-study effects.

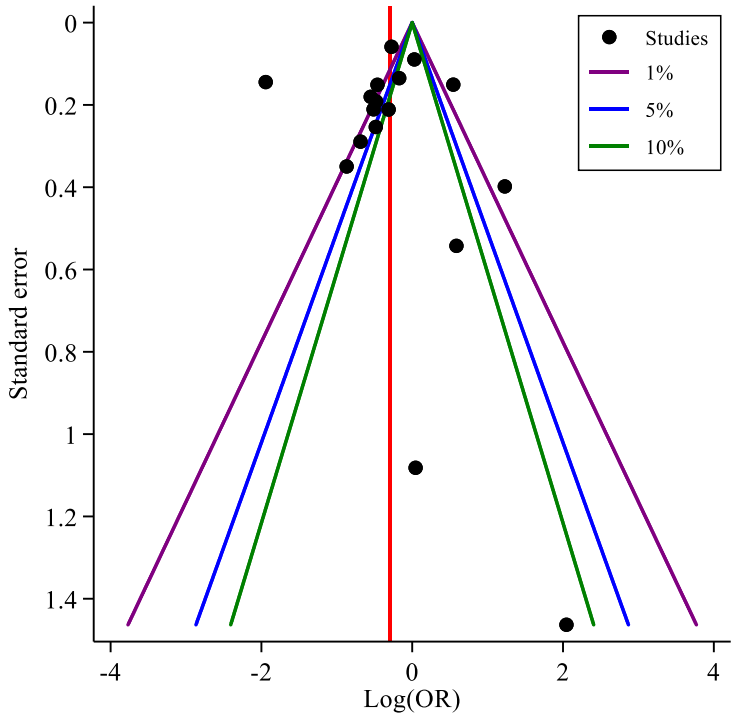


Figure 3.13. Contour-enhanced funnel plot of the 17 cohorts comparing the risk of preterm birth in treated versus untreated HIV-positive pregnant women using unadjusted data. Solid black circles correspond to the 17 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 20 cohorts, 15 specified ART complexity: ten used both non HAART and HAART, three used non HAART and two used HAART only (Appendix 3.8: Figure 3.15 and Figure 3.16). HIV-positive women treated with non HAART (pooled OR: 0.68, 95% CI: 0.58, 0.79) (Appendix 3.8: Figure 3.15), but not HAART (pooled OR: 0.80, 95% CI: 0.52, 1.25) (Appendix 3.8: Figure 3.16), had a lower risk of PTB than those untreated. Fifteen cohorts specified ART class: 10 used both non PI and PI-based regimens and five used non PI-based regimens

only (Appendix 3.8: Figure 3.17 and Figure 3.18). HIV-positive women receiving non PI (pooled OR: 0.79, 95% CI: 0.64, 0.98) (Appendix 3.8: Figure 3.17), but not PI-based regimens (pooled OR: 0.87, 95% CI: 0.63, 1.20) (Appendix 3.8: Figure 3.18), had a lower risk of PTB than those receiving no ART. Nine cohorts specified timing of ART initiation: four included HIV-positive women initiating ART both pre-conception and post-conception and five post-conception only (Appendix 3.8: Figure 3.19 and Figure 3.20). HIV-positive women initiating ART pre-conception (pooled OR: 1.31, 95% CI: 0.60, 2.87) (Appendix 3.8: Figure 3.19) or post-conception (pooled OR: 0.98, 95% CI: 0.46, 2.06) (Appendix 3.8: Figure 3.20) showed a similar risk of PTB compared with those receiving no ART.

The meta-analysis of adjusted effect estimates of five cohorts (four retrospective and one prospective) showed a lower risk of PTB in HIV-positive women receiving any ART than those receiving no ART (pooled adjusted OR: 0.84, 95% CI: 0.74, 0.94); no heterogeneity (I^2 = 0%) was evident (Figure 3.14). Several cohorts reported adjusted effect estimates for PTB risk in women receiving non HAART (n=3), HAART (n=3), EFV-based HAART (n=2), NVP-based HAART (n=3) and PI-based HAART (n=3), compared with women receiving no ART (Figure 3.15). Women receiving PI-based HAART (pooled adjusted OR: 2.52, 95% CI: 1.03, 6.13), but not other ART regimens, showed a higher risk of PTB than women receiving no ART (Figure 3.15).

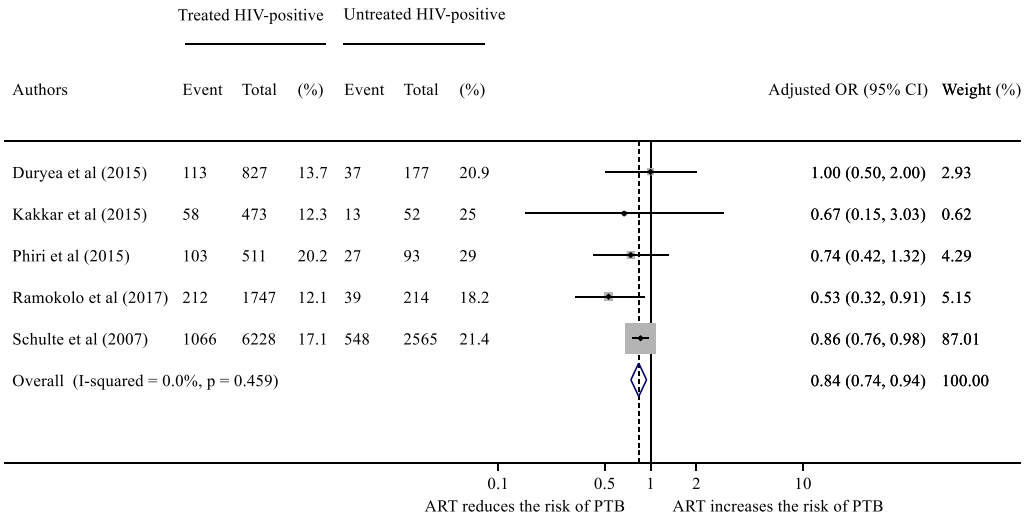


Figure 3.14. Forest plot of risk of preterm birth in treated versus untreated HIV-positive pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

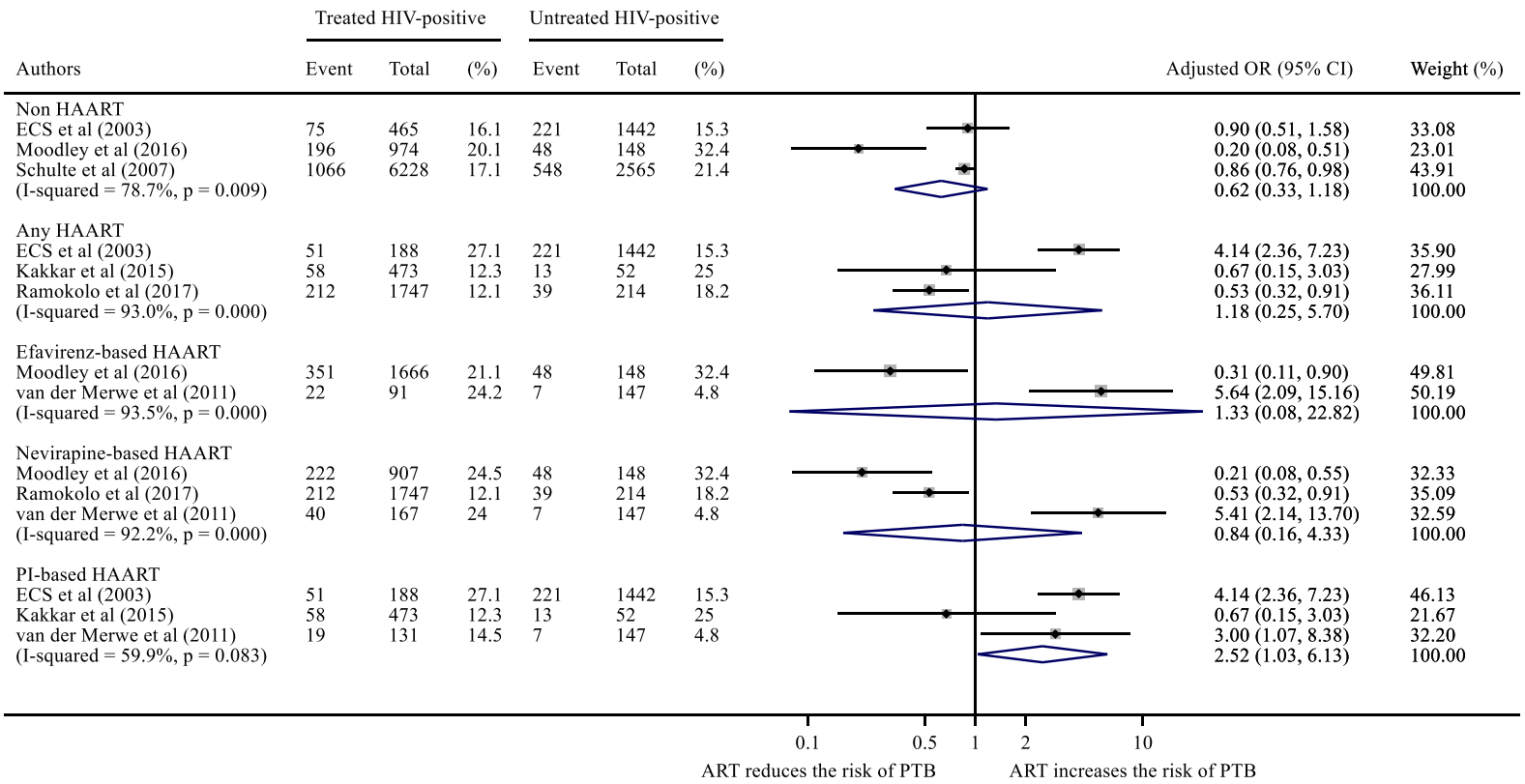


Figure 3.15. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with various ART regimens versus untreated HIV-positive pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

3.4.4.1.2 Spontaneous preterm birth (sPTB)

A retrospective cohort conducted in a high-income country, including 1,869 women, showed that HIV-positive women treated with any ART had a lower risk of sPTB than those untreated (OR: 0.39, 95% CI: 0.20, 0.73) [372].

3.4.4.1.3 Very preterm birth (VPTB)

A prospective cohort conducted in a high-income country, including 1,180 women, showed no difference in VPTB risk between HIV-positive women on treatment and those not on treatment (OR: 1.89, 95% CI: 0.82, 4.36) [370].

3.4.4.2 Effect of maternal ART on birth weight

3.4.4.2.1 Low birth weight (LBW)

The meta-analysis of unadjusted effect estimates of 11 cohorts (six retrospective and five prospective), including 21,548 women, showed an association between ART and a decreased risk of LBW (pooled OR: 0.80, 95% CI: 0.68, 0.94) compared with no ART; moderate heterogeneity (I^2 = 58.1%) was observed (Figure 3.16). This association persisted in the sub-group analysis of retrospective (pooled OR: 0.69, 95% CI: 0.58, 0.84), but not prospective cohorts (pooled OR: 0.96, 95% CI: 0.75, 1.23) (Figure 3.16A), and in the sub-group analysis of cohorts in high-income country (pooled OR: 0.80, 95% CI: 0.73, 0.87) but not in LMIC (pooled OR: 0.77, 95% CI: 0.47, 1.27) (Figure 3.16B).

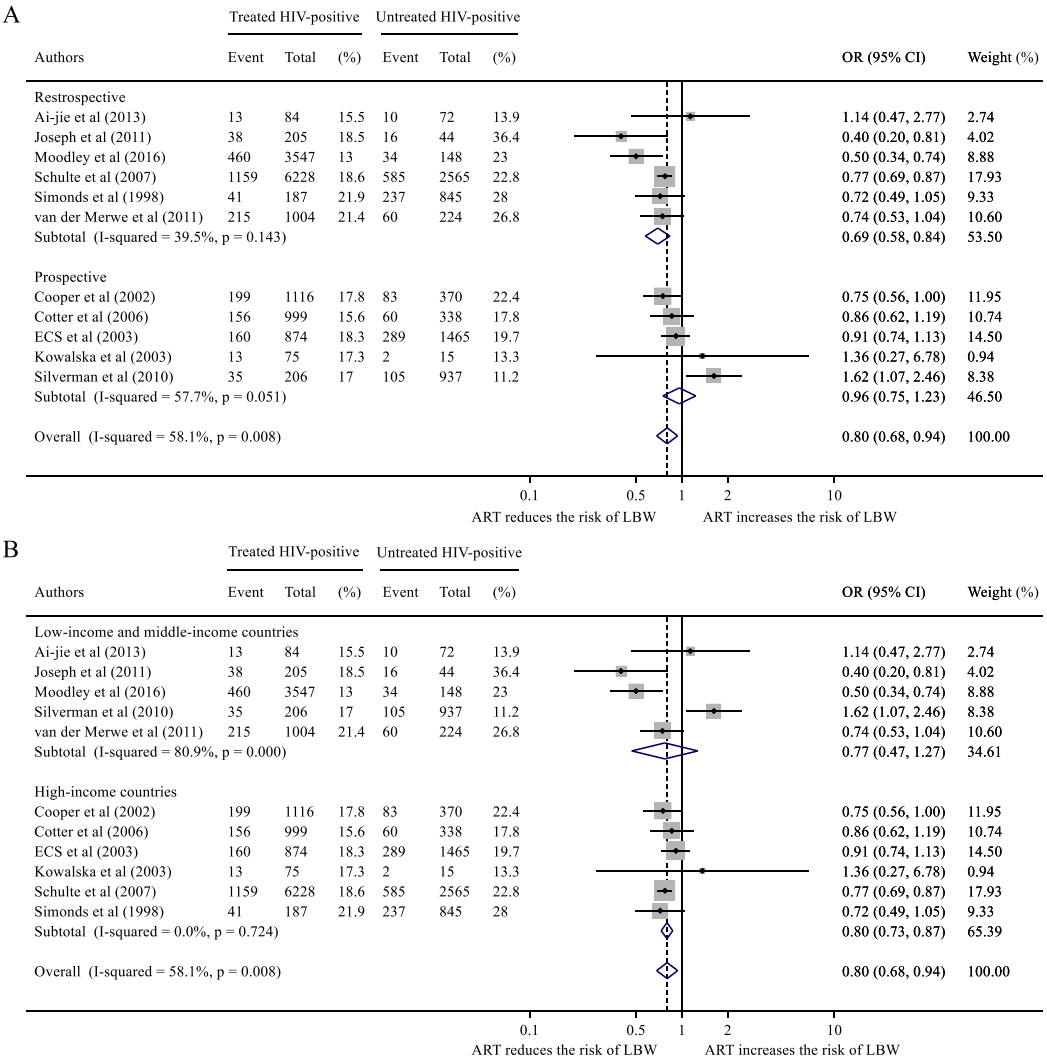


Figure 3.16. Forest plots of risk of low birth weight in treated versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

Figure 3.17 shows a symmetric contour-enhanced funnel plot, suggesting no evidence of publication bias; the *P* value of Harbord's test was 0.953 suggesting no evidence of small-study effects.

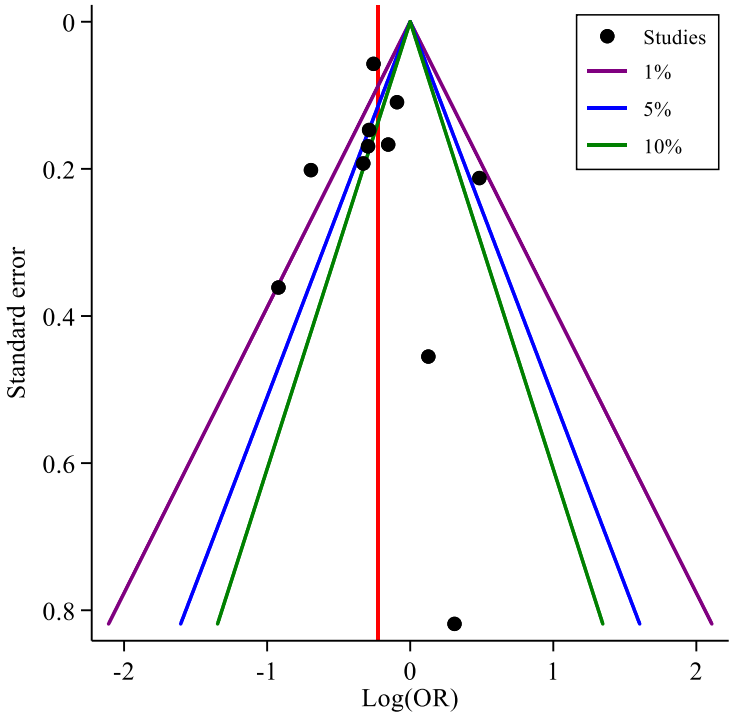


Figure 3.17. Contour-enhanced funnel plot of the 11 cohorts comparing the risk of low birth weight in treated versus untreated HIV-positive pregnant women using unadjusted data. Solid black circles correspond to the 11 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 11 cohorts, 10 specified ART complexity: five used both non HAART and HAART, two used non HAART and three used HAART only (Appendix 3.8: Figure 3.21 and Figure 3.22). HIV-positive women receiving non HAART (pooled OR: 0.72, 95% CI: 0.59, 0.89) (Appendix 3.8: Figure 3.21) or HAART (pooled OR: 0.75, 95% CI: 0.58, 0.98) (Appendix 3.8: Figure 3.22) had a lower risk of LBW than those receiving no treatment. Ten cohorts specified ART class: four used both non PI and PI-based regimens, five used non PI and one used PI-based regimens only (Appendix 3.8: Figure 3.23 and Figure 3.24). HIV-positive women on non PI (pooled OR: 0.75, 95% CI: 0.65, 0.85) (Appendix 3.8: Figure 3.23), but not PI-based regimens (pooled OR: 0.86, 95% CI: 0.60, 1.24)

(Appendix 3.8: Figure 3.24), had a lower risk of LBW compared with women on no ART. All women initiated ART post-conception.

Several cohorts reported adjusted effect estimates for the effects of EFV (n=2), NVP (n=3) and PI-based HAART (n=1) on LBW risk: none of these regimens were associated with LBW compared with no treatment (Figure 3.18).

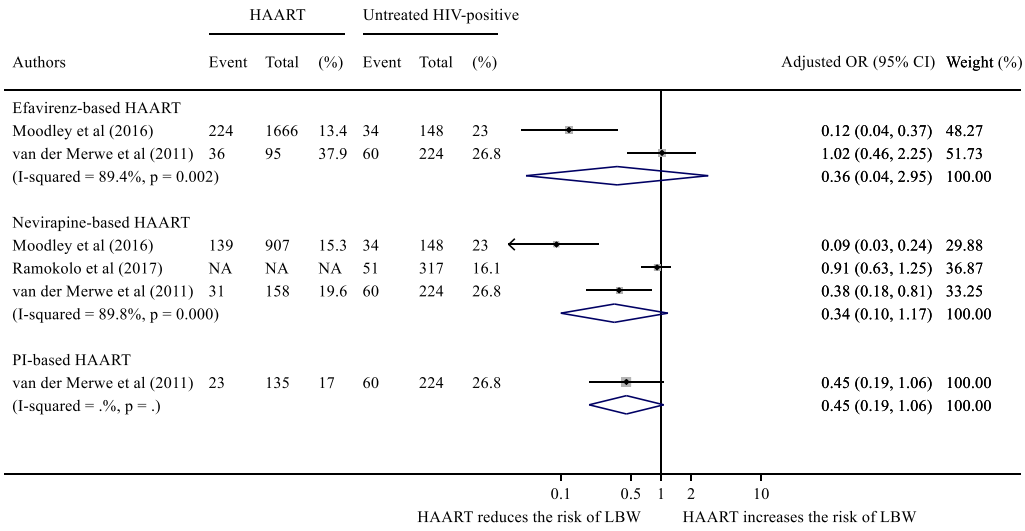


Figure 3.18. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with efavirenze, nevirapine and PI-based HAART versus untreated HIV-positive pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; NA, not available; OR, odds ratio; PI, protease inhibitor.

3.4.4.2.2 Very low birth weight (VLBW)

The pooled unadjusted effect estimates of two cohorts, including 2,565 women, showed an association between ART and a lower risk of VLBW compared with no ART (pooled OR: 0.49, 95% CI: 0.29, 0.83) (Figure 3.19).

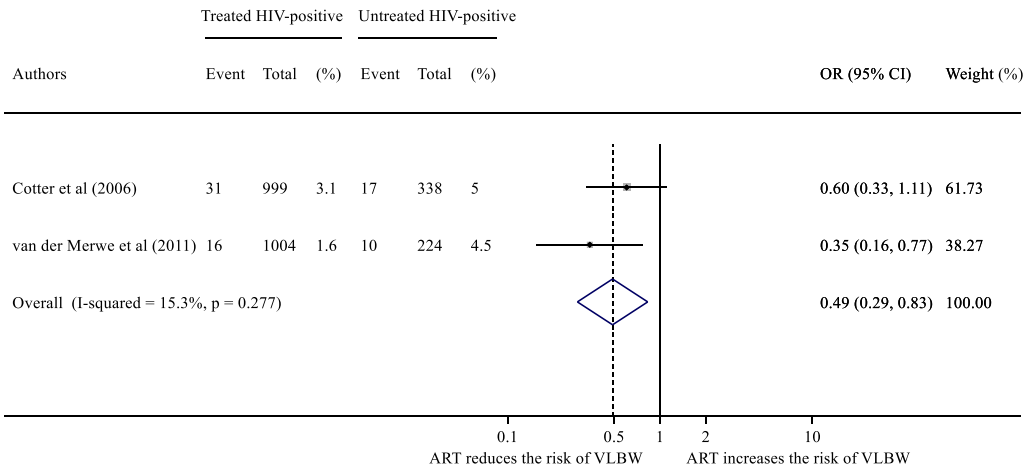


Figure 3.19. Forest plot of risk of very low birth weight in treated versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio, VLBW, very low birth weight.

3.4.4.3 Effect of maternal ART on gestational age and birth weight combined

3.4.4.3.1 Small for gestational age (SGA)

The meta-analysis of unadjusted effect estimates of three retrospective cohorts, including 5,303 women, showed no association between ART and SGA (pooled OR: 0.92, 95% CI: 0.70, 1.21) (Figure 3.20). Of these three cohorts, two specified ART complexity: one used both non HAART and HAART, and the other used non HAART only (Appendix 3.8: Figure 3.25). Both non HAART (pooled OR: 0.93, 95% CI: 0.56, 1.55) (Appendix 3.8: Figure 3.25A) and HAART (one study, OR: 0.81, 95% CI: 0.47, 1.41) (Appendix 3.8: Figure 3.25B) were not associated with SGA compared with no ART. Three cohorts specified ART class: two used both non PI and PI-based regimens, and one used non PI-based regimens only (Appendix 3.8: Figure 3.26). Both non PI (pooled OR: 1.00, 95% CI: 0.74, 1.34)

(Appendix 3.8: Figure 3.26A) and PI-based regimens (pooled OR: 0.90, 95% CI: 0.65, 1.26) (Appendix 3.8: Figure 3.26B) were not associated with SGA compared with no ART.

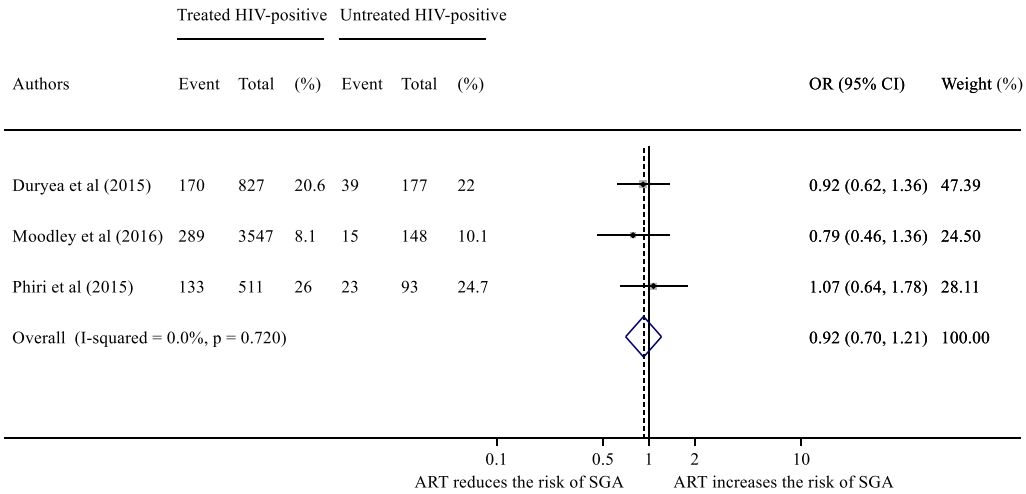


Figure 3.20. Forest plot of risk of small for gestational age in treated versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio, SGA, small for gestational age.

Three retrospective cohorts were included in the meta-analysis of adjusted effect estimates, and showed no association between ART and SGA (pooled adjusted OR: 1.09, 95% CI: 0.80, 1.48) (Figure 3.21).

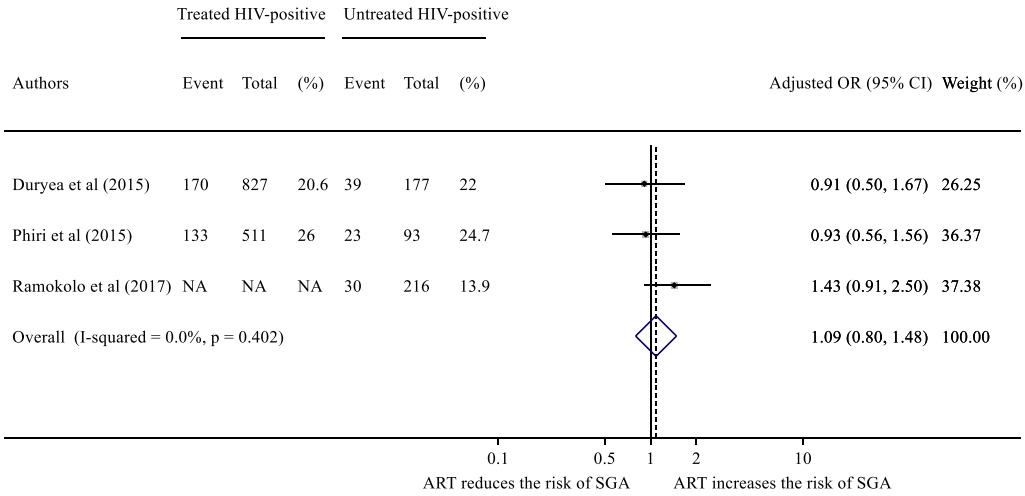


Figure 3.21. Forest plot of risk of small for gestational age in treated versus untreated HIV-positive pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; SGA, small for gestational age.

Several cohorts reported adjusted effect estimates for the risk of SGA in HIV-positive women on monotherapy (n=2), and EFV (n=1) and NVP-based HAART (n=2) compared with HIV-positive women not on ART (Figure 3.22). None of these ART regimens were associated with SGA, except for EFV-based HAART, which was associated with a decreased risk of SGA (adjusted OR: 0.25, 95% CI: 0.07, 0.88); however only one study [28] reported this association (Figure 3.22).

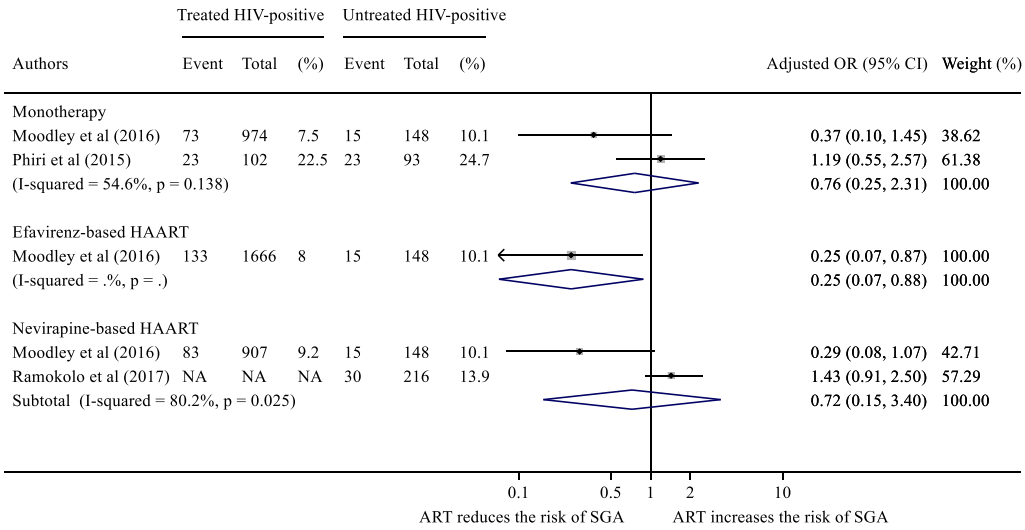


Figure 3.22. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with monotherapy, and efavirenz and nevirapine-based HAART versus untreated HIV-positive pregnant women using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; SGA, small for gestational age.

3.4.4.3.2 Very small for gestational age (VSGA)

The pooled unadjusted effect estimates of two cohorts, including 3,494 women, showed no difference in VSGA risk between HIV-positive women on treatment and those not on treatment (pooled OR: 1.31, 95% CI: 0.60, 2.84) (Figure 3.23). Being treated with non HAART (pooled OR: 1.35, 95% CI: 0.93, 1.95) (Appendix 3.8: Figure 3.27A) and HAART (pooled OR: 1.48, 95% CI: 0.47, 4.72) (Appendix 3.8: Figure 3.27B) were not associated with VSGA compared with being untreated during pregnancy.

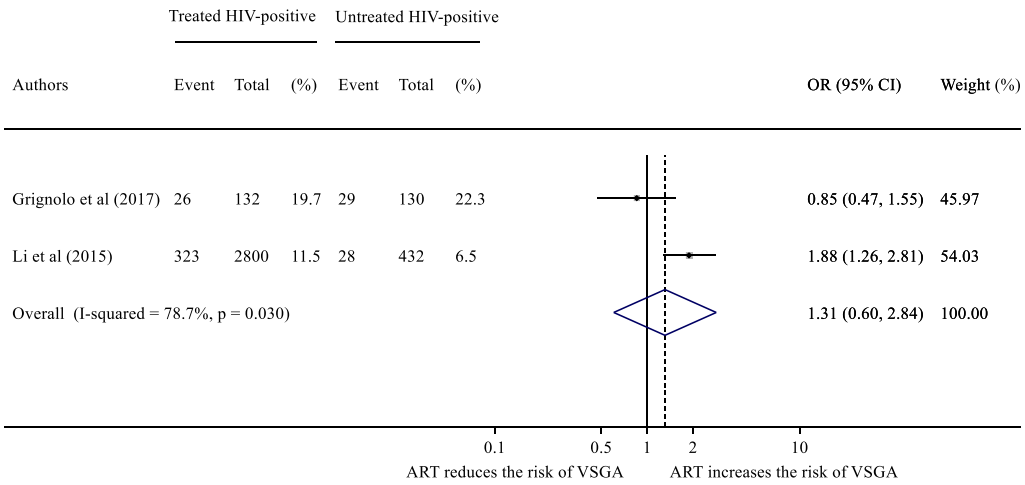


Figure 3.23. Forest plot of risk of very small for gestational age in treated versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio, VSGA, very small for gestational age

3.4.4.4 Effect of maternal ART on fetal and neonatal mortality

No studies reported the outcomes of fetal and neonatal mortality in treated versus untreated HIV-positive pregnant women.

3.4.4.5 Effect of maternal ART on mother-to-child transmission (MTCT)

The outcome of MTCT was reported in four cohorts (two retrospective and two prospective), including 5,429 women: one was conducted in an LMIC and three in a high-income country (Figure 3.24). HIV-positive women receiving any ART had a lower risk of MTCT than those receiving no ART (pooled OR: 0.31, 95% CI: 0.25, 0.37), with no heterogeneity (I^2 = 0%) (Figure 3.24). This association persisted irrespective of cohort design: retrospective (pooled OR: 0.30, 95% CI: 0.22, 0.40) and prospective (pooled OR: 0.32, 95% CI: 0.23, 0.44) (Figure 3.24).

Sub-group analysis by country-income status was not performed because, of the four cohorts, only one was conducted in an LMIC [30].

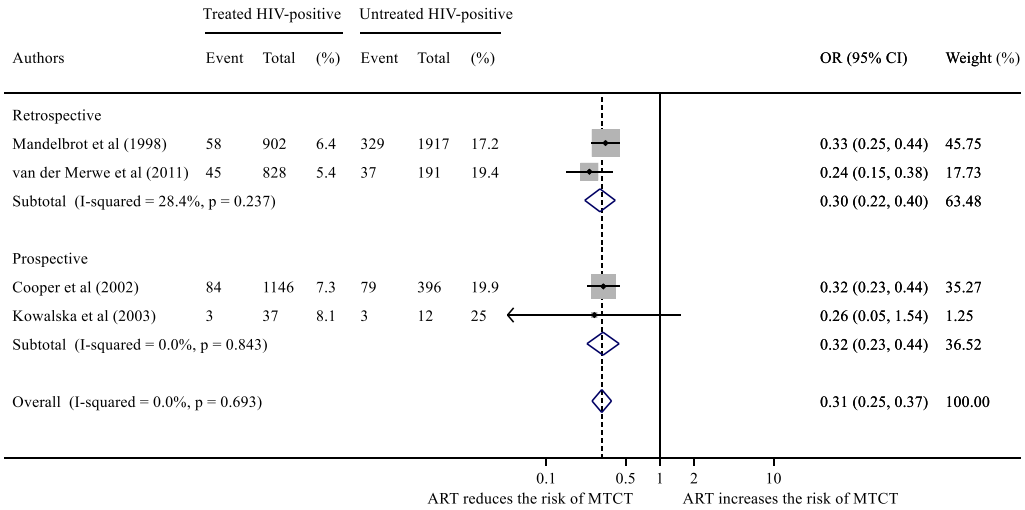


Figure 3.24. Forest plot of risk of mother-to-child transmission in treated versus untreated HIV-positive pregnant women using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

Of the four cohorts, regarding ART complexity, two used both non HAART and HAART, one used non HAART and one used HAART only (Appendix 3.8: Figure 3.28). Both non HAART (pooled OR: 0.36, 95% CI: 0.29, 0.45) (Appendix 3.8: Figure 3.28A) and HAART (pooled OR: 0.11, 95% CI: 0.02, 0.47) (Appendix 3.8: Figure 3.28B) were associated with a lower risk of MTCT than no treatment. Regarding ART class, two used both non PI and PI-based regimens, and two used non PI-based regimens only (Appendix 3.8: Figure 3.29). Both non PI (pooled OR: 0.35, 95% CI: 0.28, 0.42) (Appendix 3.8: Figure 3.29A) and PI-based regimens (pooled OR: 0.24, 95% CI: 0.14, 0.43) (Appendix 3.8: Figure 3.29B) were associated with a lower risk of MTCT than no treatment.

3.4.4.6 Summary of meta-analysis results

The summary of meta-analysis results for the effect of maternal ART on perinatal outcomes is provided in Appendix 3.8: Tables 3.4 and 3.5.

3.4.5 Effect of ART complexity on perinatal outcomes

The third aim was investigated by conducting pairwise meta-analyses assessing the risk of adverse perinatal outcomes in HIV-positive pregnant women receiving different ART complexities: monotherapy, dual therapy and HAART.

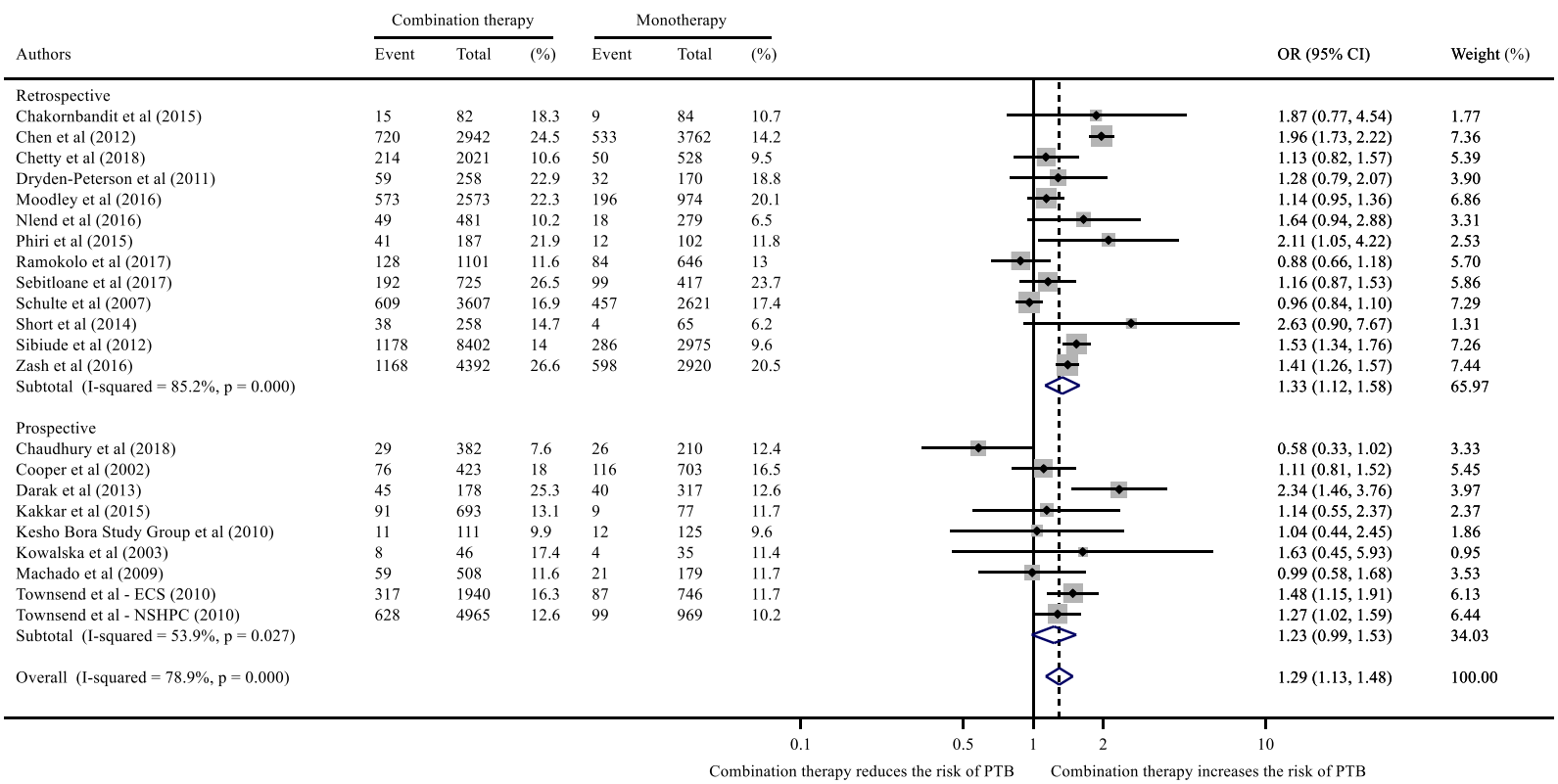
3.4.5.1 Effect of ART complexity on gestational age at delivery

3.4.5.1.1 Preterm birth (PTB)

Combination therapy versus monotherapy

The exposure group was HIV-positive pregnant women receiving any combination therapy, with women receiving monotherapy the comparator group. PTB was reported by 23 cohorts (13 retrospective and 10 prospective), including 57,593 women; 12 cohorts were conducted in LMICs and 11 in high-income countries. One prospective cohort [383] conducted in high-income countries, including 2,414 women, was excluded due to the possibility of overlap with another cohort [19]. HIV-positive women receiving any combination therapy had a higher risk of PTB than those receiving monotherapy (pooled OR: 1.29, 95% CI: 1.13, 1.48), with a high degree of heterogeneity (I^2 = 78.9%) (Figure 3.25). This association remained in the sub-group analysis of retrospective (pooled OR: 1.33, 95% CI: 1.12, 1.58), but not prospective cohorts (pooled OR: 1.23, 95% CI: 0.99, 1.53); a high degree of heterogeneity (I^2 = 85.2%) was observed in the retrospective cohorts only (Figure 3.25A). Combination therapy remained associated with an increased risk of PTB irrespective of country-income status: LMIC (pooled OR: 1.29, 95% CI: 1.06, 1.56) and high-income country (pooled OR: 1.29, 95% CI: 1.07, 1.55); a high degree of heterogeneity (I^2 = 82%) was observed in LMIC only (Figure 3.25B).

A


Combination therapy
Monotherapy
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Chakornbandit et al (2015) 15 82 18.3 9 84 10.7 1.87 (0.77, 4.54) 1.77
Chen et al (2012) 720 2942 24.5 533 3762 14.2 1.96 (1.73, 2.22) 7.36
Chetty et al (2018) 214 2021 10.6 50 528 9.5 1.13 (0.82, 1.57) 5.39
Dryden-Peterson et al (2011) 59 258 22.9 32 170 18.8 1.28 (0.79, 2.07) 3.90
Moodley et al (2016) 573 2573 22.3 196 974 20.1 1.14 (0.95, 1.36) 6.86
Nlend et al (2016) 49 481 10.2 18 279 6.5 1.64 (0.94, 2.88) 3.31
Phiri et al (2015) 41 187 21.9 12 102 11.8 2.11 (1.05, 4.22) 2.53
Ramokolo et al (2017) 128 1101 11.6 84 646 13 0.88 (0.66, 1.18) 5.70
Sebitloane et al (2017) 192 725 26.5 99 417 23.7 1.16 (0.87, 1.53) 5.86
Schulte et al (2007) 609 3607 16.9 457 2621 17.4 0.96 (0.84, 1.10) 7.29
Short et al (2014) 38 258 14.7 4 65 6.2 2.63 (0.90, 7.67) 1.31
Sibiude et al (2012) 1178 8402 14 286 2975 9.6 1.53 (1.34, 1.76) 7.26
Zash et al (2016) 1168 4392 26.6 598 2920 20.5 1.41 (1.26, 1.57) 7.44
Subtotal (I-squared = 85.2%, p = 0.000) 1.33 (1.12, 1.58) 65.97
Prospective
Chaudhury et al (2018) 29 382 7.6 26 210 12.4 0.58 (0.33, 1.02) 3.33
Cooper et al (2002) 76 423 18 116 703 16.5 1.11 (0.81, 1.52) 5.45
Darak et al (2013) 45 178 25.3 40 317 12.6 2.34 (1.46, 3.76) 3.97
Kakkar et al (2015) 91 693 13.1 9 77 11.7 1.14 (0.55, 2.37) 2.37
Kesho Bora Study Group et al (2010) 11 111 9.9 12 125 9.6 1.04 (0.44, 2.45) 1.86
Kowalska et al (2003) 8 46 17.4 4 35 11.4 1.63 (0.45, 5.93) 0.95
Machado et al (2009) 59 508 11.6 21 179 11.7 0.99 (0.58, 1.68) 3.53
Townsend et al - ECS (2010) 317 1940 16.3 87 746 11.7 1.48 (1.15, 1.91) 6.13
Townsend et al - NSHPC (2010) 628 4965 12.6 99 969 10.2 1.27 (1.02, 1.59) 6.44
Subtotal (I-squared = 53.9%, p = 0.027) 1.23 (0.99, 1.53) 34.03
Overall (I-squared = 78.9%, p = 0.000) 1.29 (1.13, 1.48) 100.00
0.1
0.5
1
2
10
Combination therapy reduces the risk of PTB
Combination therapy increases the risk of PTB

B

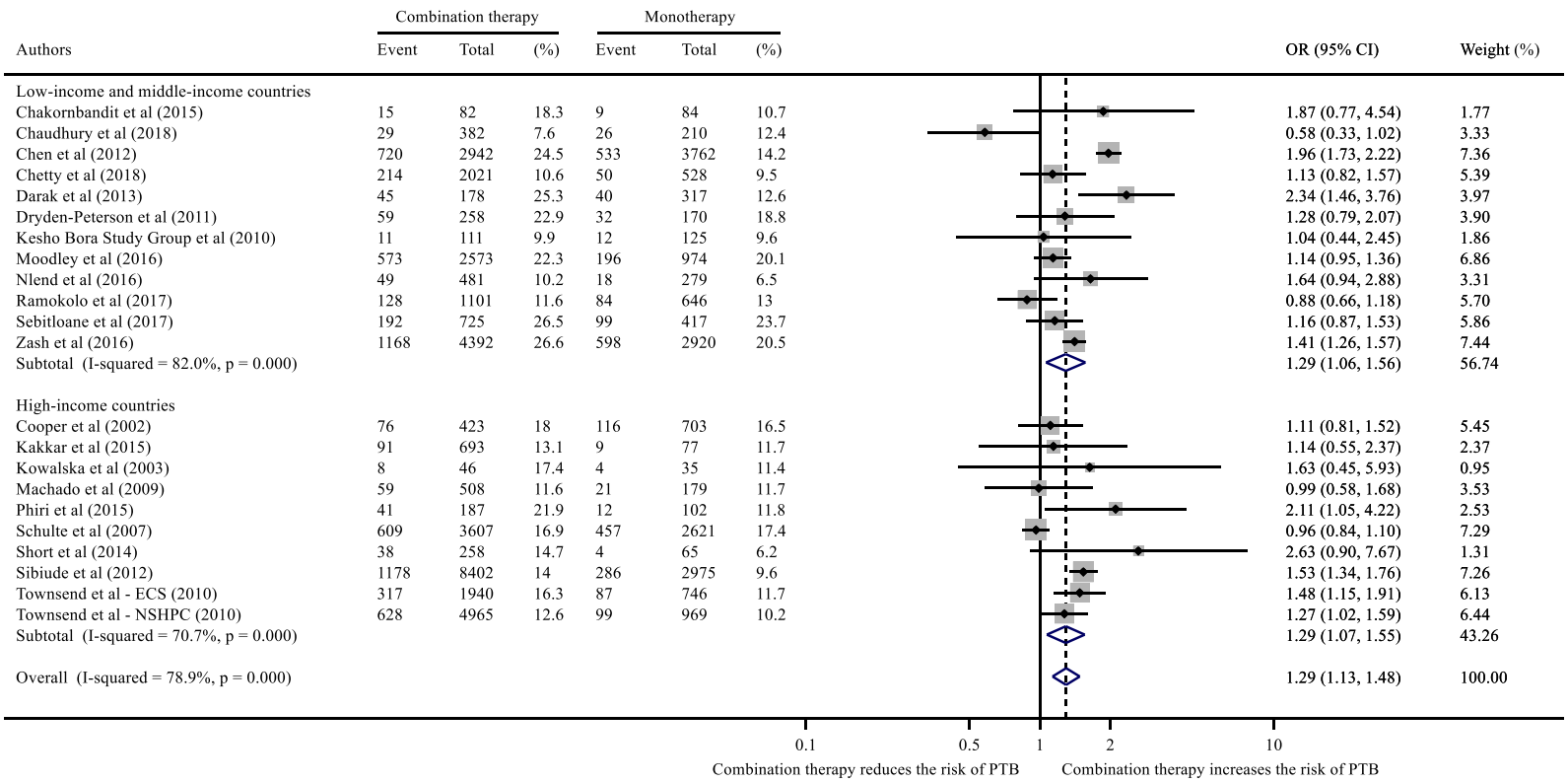


Figure 3.25. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

The contour-enhanced funnel plot seems symmetric (Figure 3.26), suggesting no evidence of publication bias; Harbord's test showed a *P* value of 0.527, suggesting no evidence of small-study effects.

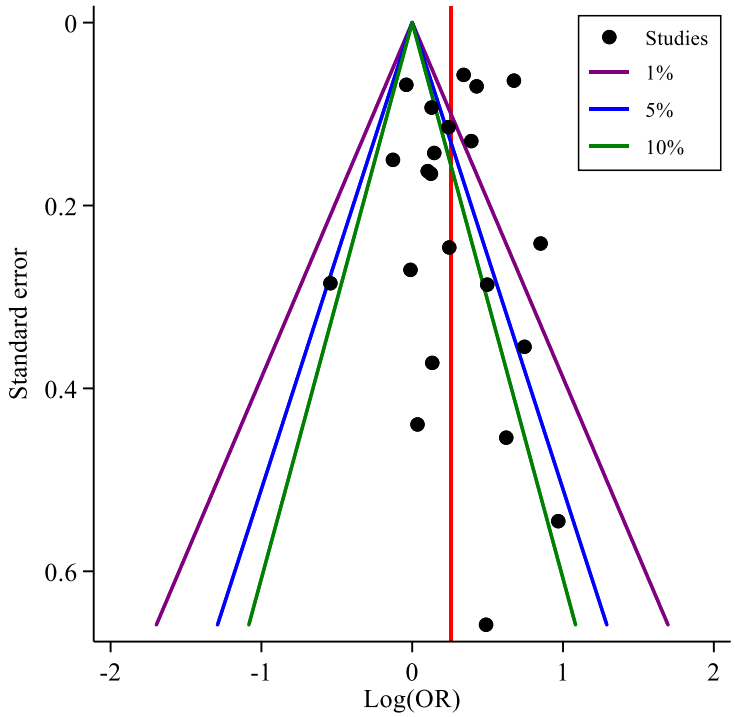


Figure 3.26. Contour-enhanced funnel plot of the 22 cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data. Solid black circles correspond to the 22 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The majority of cohorts (18 of 23) used ZDV as a monotherapy agent, while others did not specify the ARV drug. For combination therapy, 15 cohorts specified ART class: six used both non PI and PI-based regimens, eight used non PI and one PI-based regimens only (Appendix 3.9: Figure 3.30 and Figure 3.31). Both non PI (pooled OR: 1.24, 95% CI: 1.04, 1.49) (Appendix 3.9: Figure 3.30) and PI-based combination therapy (pooled OR: 1.93, 95% CI: 1.49, 2.50)

(Appendix 3.9: Figure 3.31) were associated with a higher risk of PTB compared with monotherapy.

Dual therapy versus monotherapy

The exposure group was HIV-positive pregnant women receiving dual therapy, and the comparator group was those receiving monotherapy. The pooled unadjusted effect estimates of eight cohorts (four retrospective and four prospective) conducted in high-income countries, including 12,040 women, showed no difference in PTB risk between dual therapy and monotherapy (pooled OR: 0.99, 95% CI: 0.80, 1.23), with a moderate heterogeneity (I^2 = 51.1%) (Figure 3.27). This finding persisted irrespective of cohort design: retrospective (pooled OR: 1.09, 95% CI: 0.74, 1.61) and prospective (pooled OR: 0.95, 95% CI: 0.74, 1.21). A high degree of heterogeneity (I^2 = 75.5%) was observed in retrospective; however no heterogeneity (I^2 = 0%) in prospective cohorts (Figure 3.27).

Of the eight cohorts, three specified ART class: all used non PI-based dual therapy; thus the effect of dual therapy on PTB risk according to ART class (non PI and PI-based) could not be explored.

The pooled adjusted effect estimates of four cohorts (one retrospective and three prospective) showed no difference in PTB risk between dual therapy and monotherapy (pooled adjusted OR: 0.99, 95% CI: 0.69, 1.43) (Figure 3.28).

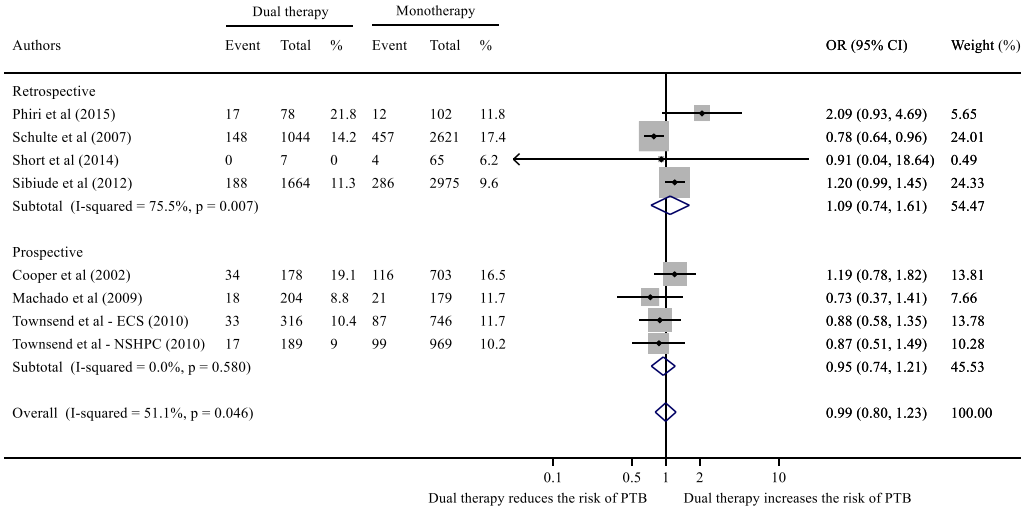


Figure 3.27. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with dual therapy versus monotherapy using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

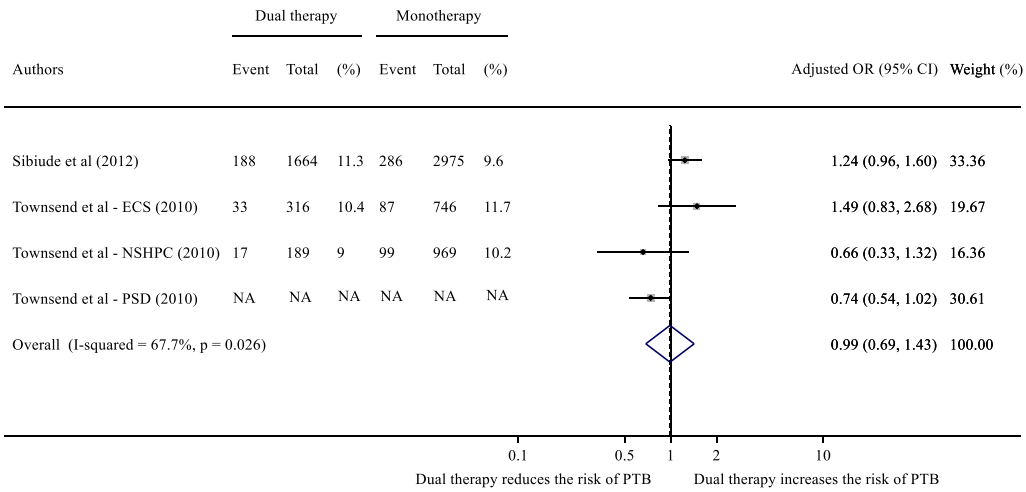


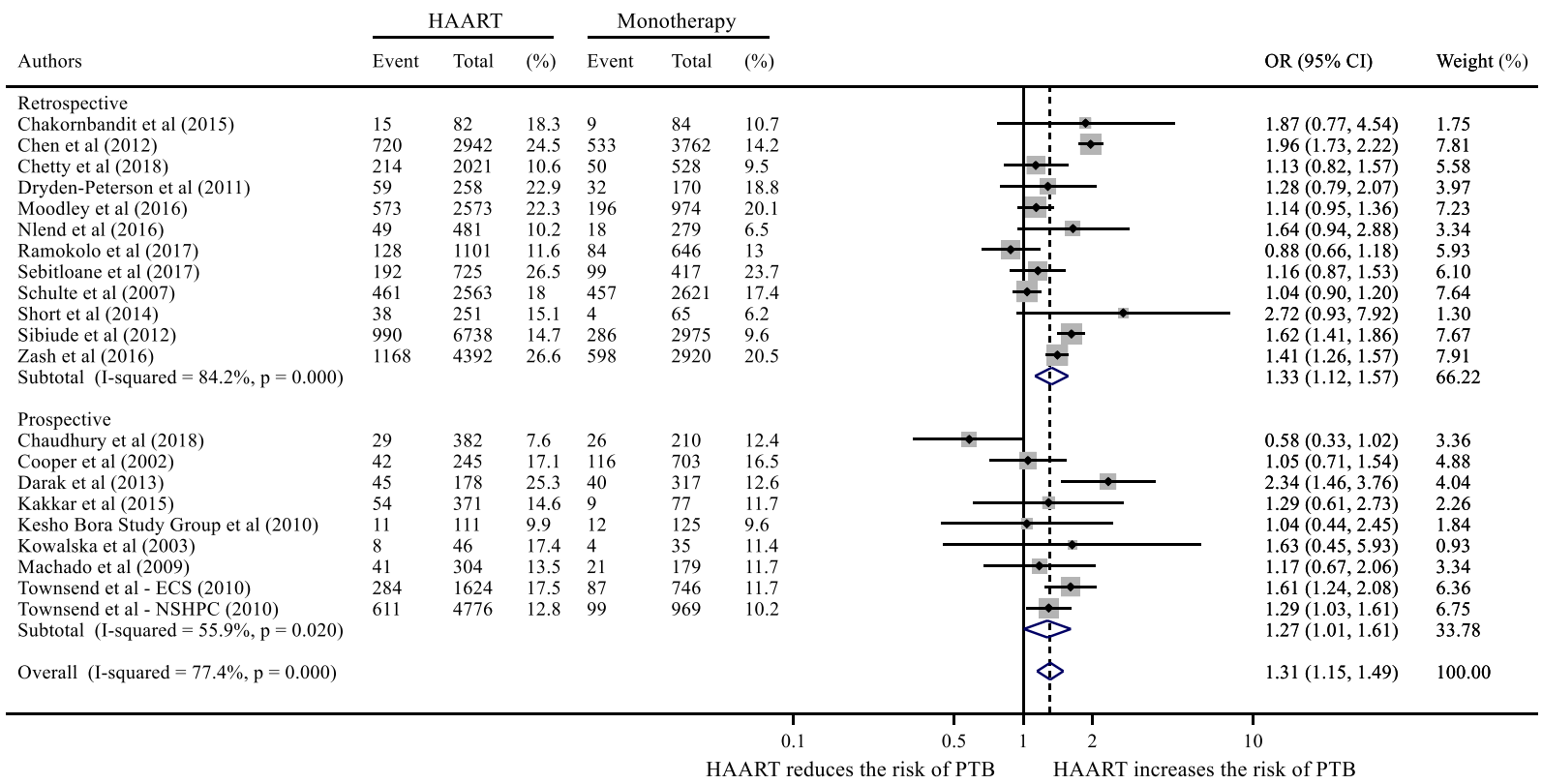
Figure 3.28. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with dual therapy versus monotherapy using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; PTB, preterm birth.

HAART versus monotherapy

The exposure group was HIV-positive pregnant women on HAART, and the comparator group was women on monotherapy. The risk of PTB in HIV-positive women on HAART versus monotherapy was reported in 21 cohorts (12 retrospective and nine prospective), including 50,966 women; 12 cohorts were conducted in LMICs and nine in high-income countries. HAART was associated with an increased risk of PTB compared with monotherapy (pooled OR: 1.31, 95% CI: 1.15, 1.49), with a high degree of heterogeneity (I^2 = 77.4%) (Figure 3.29). The association was consistently observed across cohort design: retrospective (pooled OR: 1.33, 95% CI: 1.12, 1.57) and prospective (pooled OR: 1.27, 95% CI: 1.01, 1.61); a high degree of heterogeneity (I^2 = 84.2%) was observed in retrospective cohorts only (Figure 3.29A). The association persisted irrespective of country-income status: LMIC (pooled OR: 1.29, 95% CI: 1.06, 1.56) and high-income country (pooled OR: 1.33, 95% CI: 1.10, 1.60); a high degree of heterogeneity (I^2 = 82%) was observed in LMIC only (Figure 3.29B).

Figure 3.30 shows a rather symmetric contour-enhanced funnel plot, indicating no evidence of publication bias; a *P* value of 0.358 was obtained from the Harbord's test, suggesting no evidence of small-study effects.

A


HAART
Monotherapy
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Chakornbandit et al (2015) 15 82 18.3 9 84 10.7 1.87 (0.77, 4.54) 1.75
Chen et al (2012) 720 2942 24.5 533 3762 14.2 1.96 (1.73, 2.22) 7.81
Chetty et al (2018) 214 2021 10.6 50 528 9.5 1.13 (0.82, 1.57) 5.58
Dryden-Peterson et al (2011) 59 258 22.9 32 170 18.8 1.28 (0.79, 2.07) 3.97
Moodley et al (2016) 573 2573 22.3 196 974 20.1 1.14 (0.95, 1.36) 7.23
Nlend et al (2016) 49 481 10.2 18 279 6.5 1.64 (0.94, 2.88) 3.34
Ramokolo et al (2017) 128 1101 11.6 84 646 13 0.88 (0.66, 1.18) 5.93
Sebitloane et al (2017) 192 725 26.5 99 417 23.7 1.16 (0.87, 1.53) 6.10
Schulte et al (2007) 461 2563 18 457 2621 17.4 1.04 (0.90, 1.20) 7.64
Short et al (2014) 38 251 15.1 4 65 6.2 2.72 (0.93, 7.92) 1.30
Sibiude et al (2012) 990 6738 14.7 286 2975 9.6 1.62 (1.41, 1.86) 7.67
Zash et al (2016) 1168 4392 26.6 598 2920 20.5 1.41 (1.26, 1.57) 7.91
Subtotal (I-squared = 84.2%, p = 0.000) 1.33 (1.12, 1.57) 66.22
Prospective
Chaudhury et al (2018) 29 382 7.6 26 210 12.4 0.58 (0.33, 1.02) 3.36
Cooper et al (2002) 42 245 17.1 116 703 16.5 1.05 (0.71, 1.54) 4.88
Darak et al (2013) 45 178 25.3 40 317 12.6 2.34 (1.46, 3.76) 4.04
Kakkar et al (2015) 54 371 14.6 9 77 11.7 1.29 (0.61, 2.73) 2.26
Kesho Bora Study Group et al (2010) 11 111 9.9 12 125 9.6 1.04 (0.44, 2.45) 1.84
Kowalska et al (2003) 8 46 17.4 4 35 11.4 1.63 (0.45, 5.93) 0.93
Machado et al (2009) 41 304 13.5 21 179 11.7 1.17 (0.67, 2.06) 3.34
Townsend et al - ECS (2010) 284 1624 17.5 87 746 11.7 1.61 (1.24, 2.08) 6.36
Townsend et al - NSHPC (2010) 611 4776 12.8 99 969 10.2 1.29 (1.03, 1.61) 6.75
Subtotal (I-squared = 55.9%, p = 0.020) 1.27 (1.01, 1.61) 33.78
Overall (I-squared = 77.4%, p = 0.000) 1.31 (1.15, 1.49) 100.00
0.1
0.5
1
2
10
HAART reduces the risk of PTB
HAART increases the risk of PTB

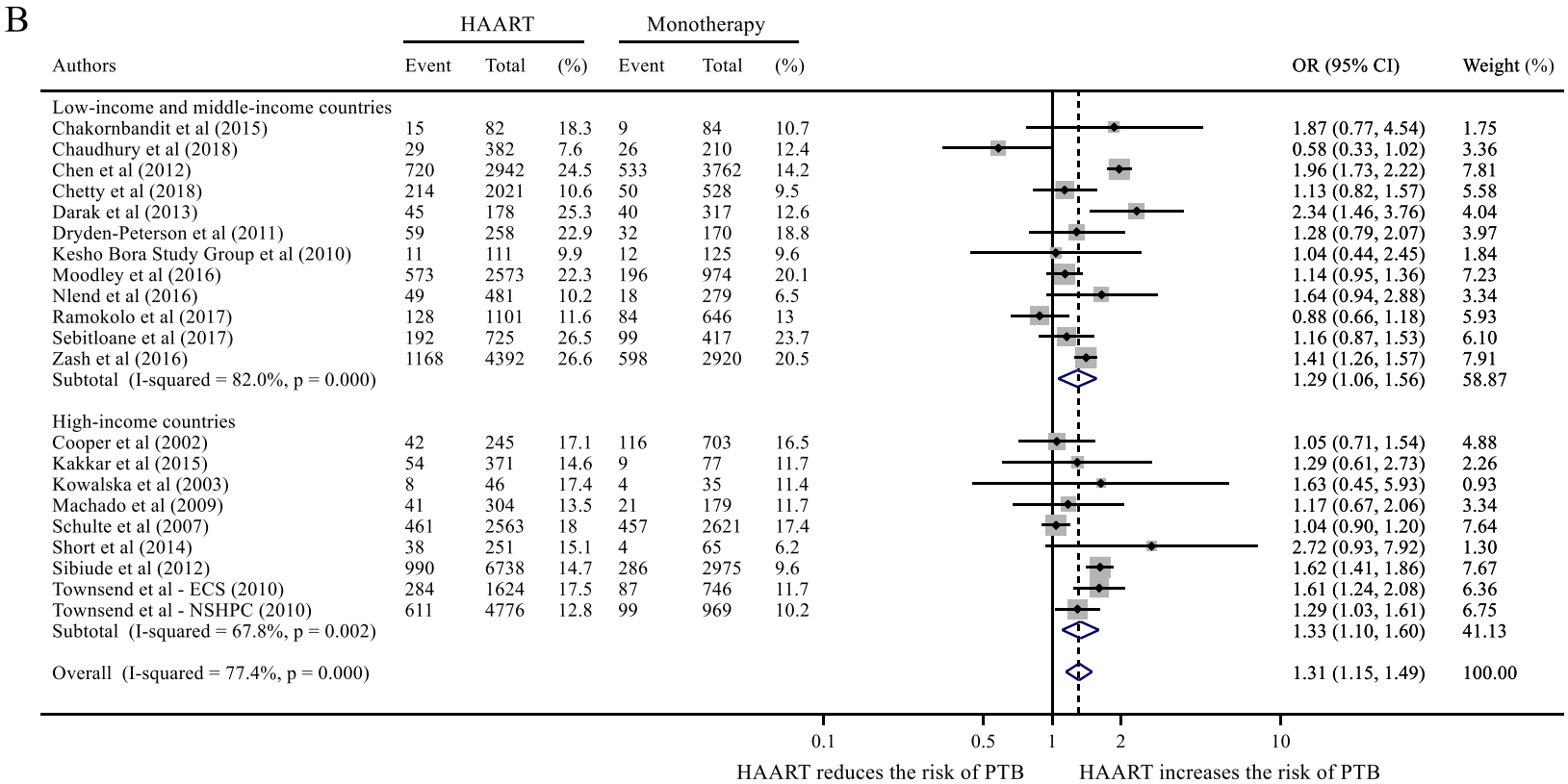


Figure 3.29. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

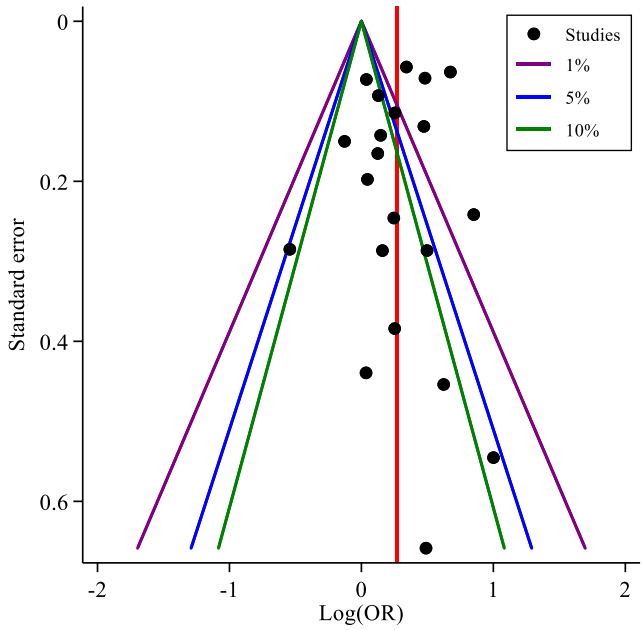


Figure 3.30. Contour-enhanced funnel plot of the 21 cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data. Solid black circles correspond to the 21 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Thirteen cohorts specified HAART class: five used both non PI and PI-based, six used non PI-based and two PI-based only (Appendix 3.9: Figure 3.32 and Figure 3.33). PI (pooled OR: 1.93, 95% CI: 1.49, 2.50) (Appendix 3.9: Figure 3.33), but not non PI-based HAART (pooled OR: 1.24, 95% CI: 0.99, 1.55) (Appendix 3.9: Figure 3.32), was associated with a higher risk of PTB compared with monotherapy.

Ten cohorts (six retrospective and four prospective) were included in the meta-analysis adjusted effect estimates. These showed an association between HAART and an increased risk of PTB (pooled adjusted OR: 1.38, 95% CI: 1.09, 1.76) compared with monotherapy; a high degree of heterogeneity (I^2 = 74.4%) was evident (Figure 3.31). Sub-group analysis by cohort design showed a borderline

significant association between HAART and PTB in both retrospective (pooled adjusted OR: 1.34, 95% CI: 0.97, 1.85) and prospective cohorts (pooled adjusted OR: 1.50, 95% CI: 0.94, 2.38) (Figure 3.31A). Sub-group analysis by country-income status showed an association between HAART and an increased risk of PTB in high-income country (pooled adjusted OR: 1.60, 95% CI: 1.14, 2.25), but not in LMIC (pooled adjusted OR: 1.17, 95% CI: 0.80, 1.72) (Figure 3.31B).

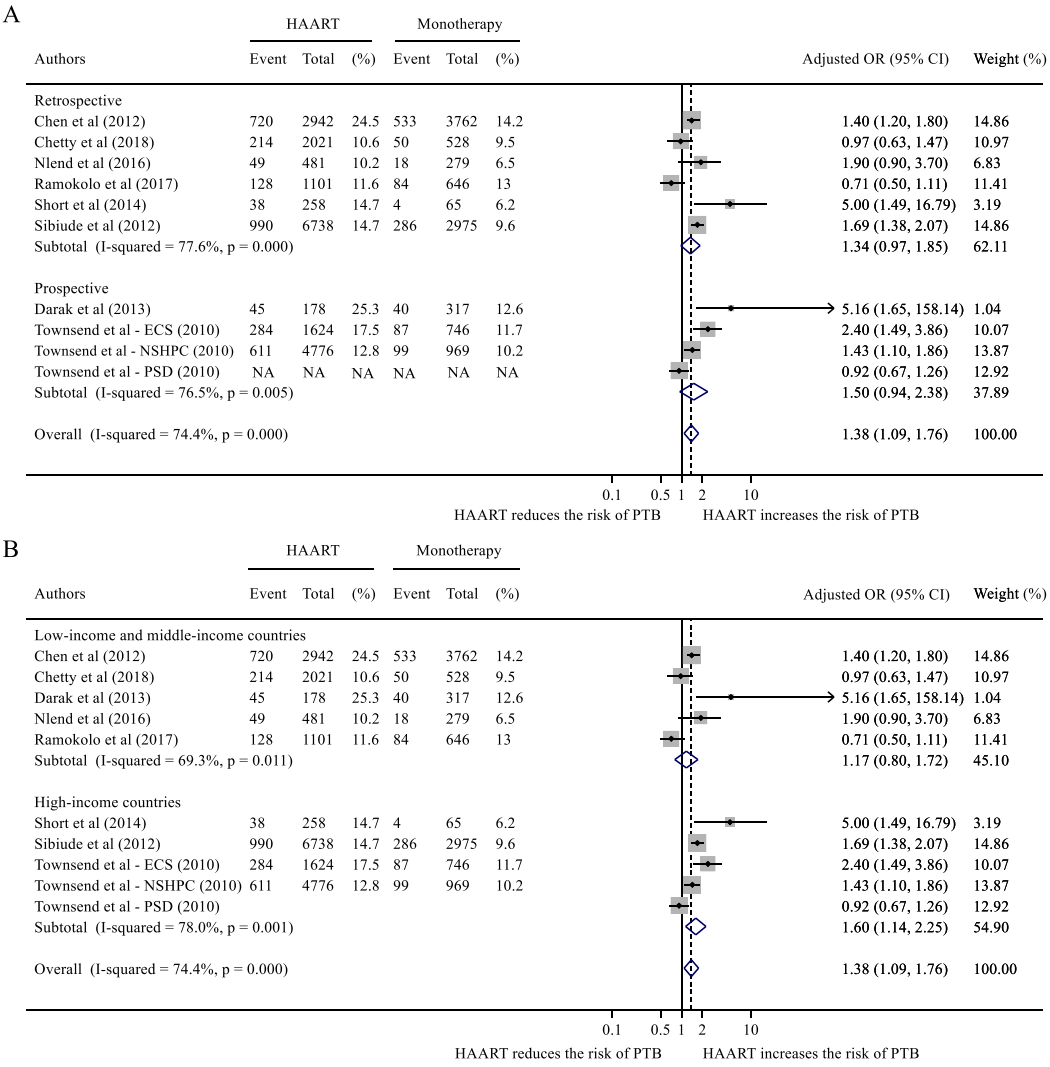


Figure 3.31. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus monotherapy using adjusted effect estimates, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; PTB, preterm birth.

HAART versus dual therapy

The exposure group was HIV-positive pregnant women treated with HAART and the comparator group was women treated with dual therapy. The meta-analysis of unadjusted effect estimates in seven cohorts (three retrospective and four prospective), conducted in high-income countries, including 20,103 women, showed that HAART was associated with a higher risk of PTB than dual therapy (pooled OR: 1.37, 95% CI: 1.22, 1.53); no heterogeneity (I^2 = 0%) was evident (Figure 3.32). This association remained irrespective of cohort design: retrospective (pooled OR: 1.34, 95% CI: 1.18, 1.53) and prospective (pooled OR: 1.42, 95% CI: 1.02, 1.96) (Figure 3.32). One study reported an adjusted effect estimate suggesting an association between HAART and an increased risk of PTB compared with dual therapy (adjusted OR: 1.21, 95% CI: 1.04, 1.40) [371].

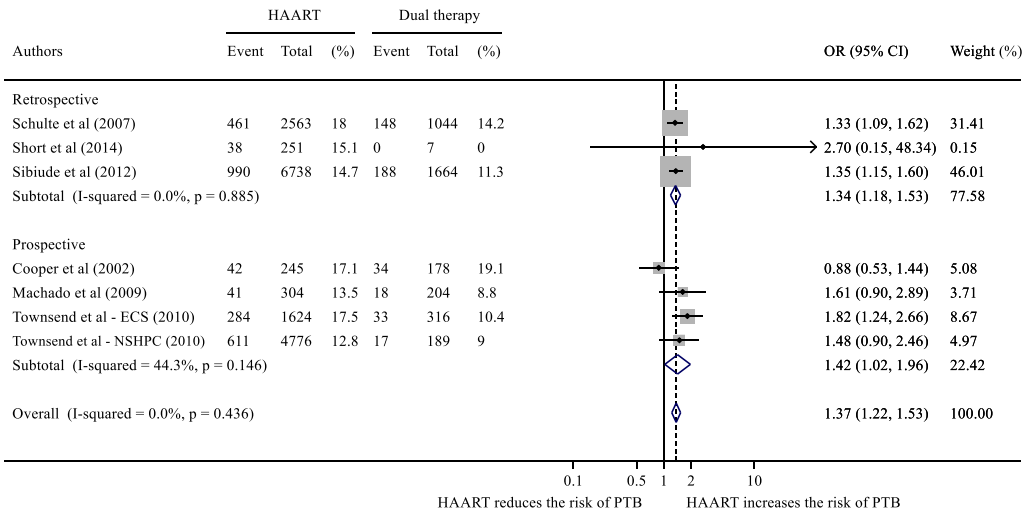


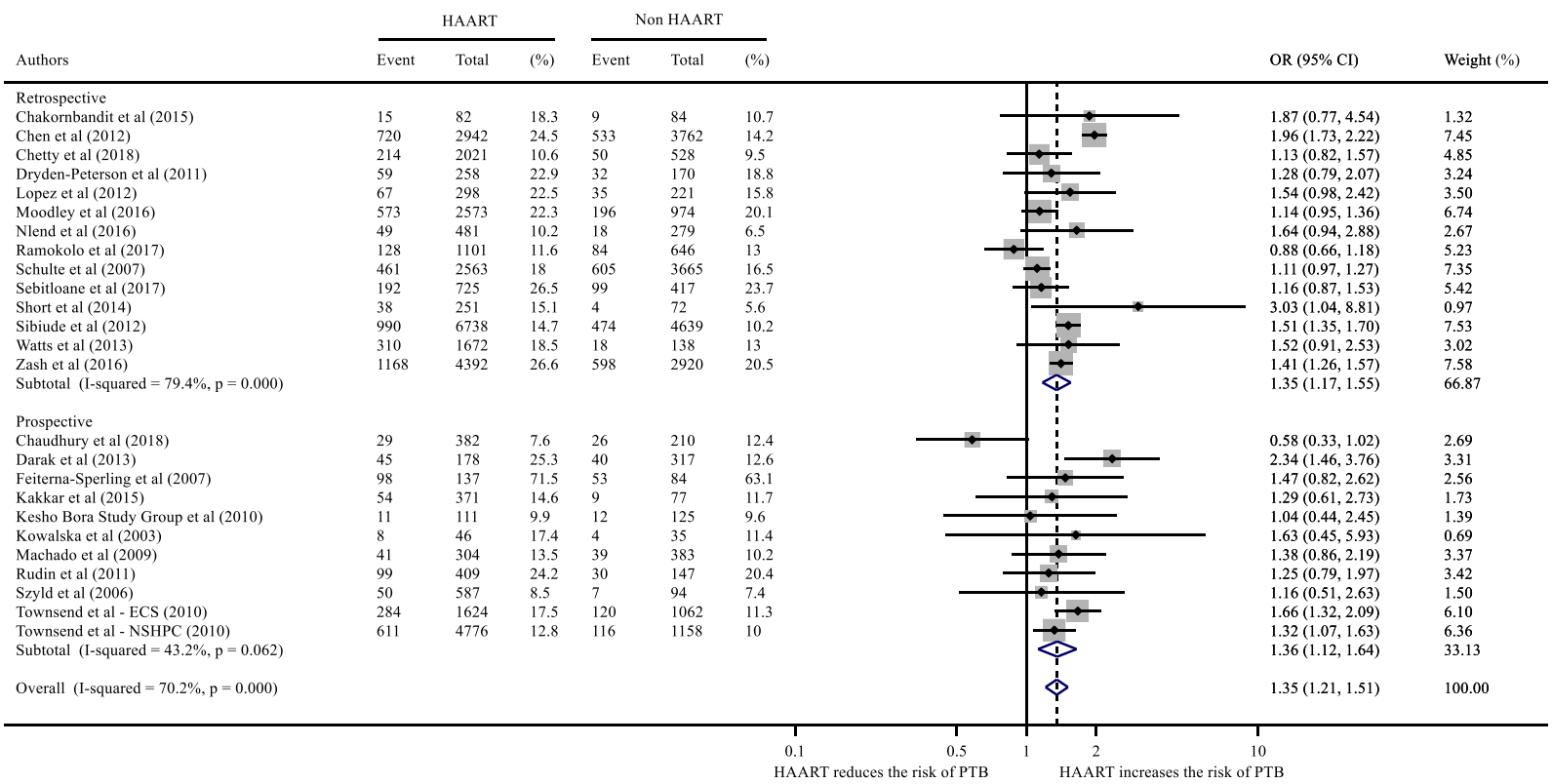
Figure 3.32. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with HAART versus dual therapy using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

HAART versus non HAART

The exposure group was HIV-positive pregnant women receiving HAART and the comparator group was women receiving non HAART. The risk of PTB in women receiving HAART versus non HAART was reported in 26 cohorts (14 retrospective and 12 prospective), including 59,643 women; 13 cohorts were conducted in LMICs and 13 in high-income countries. One prospective cohort [383] conducted in high-income countries, including 2,414 women, was excluded due to the possibility of overlap with another cohort [19]. HAART was associated with a higher risk of PTB than non HAART (pooled OR: 1.35, 95% CI: 1.21, 1.51), with moderate heterogeneity (I^2 = 70.2%) (Figure 3.33). This association was consistently observed across cohort design and country income status: retrospective (pooled OR: 1.35, 95% CI: 1.17, 1.55) and prospective (pooled OR: 1.36, 95% CI: 1.12, 1.64) (Figure 3.33A); LMIC (pooled OR: 1.28, 95% CI: 1.06, 1.55) and high-income country (pooled OR: 1.39, 95% CI: 1.24, 1.57) (Figure 3.33B). A high degree of heterogeneity was observed in retrospective cohorts (I^2 = 79.4%) (Figure 3.33A) and LMIC (I^2 = 80.5%) (Figure 3.33B).

The contour-enhanced funnel plot of the 25 cohorts seems symmetric (Figure 3.34), suggesting no evidence of publication bias; the Harbord's test showed a *P* value of 0.471, suggesting no evidence of small-study effects. Contour-enhanced funnel plots by cohort design (retrospective and prospective) (Appendix 3.9: Figure 3.34), and by country-income status (LMIC and high-income country) (Appendix 3.9: Figure 3.35) show similar findings with those observed in the 25 cohorts.

A


HAART
Non HAART
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Chakornbandit et al (2015) 15 82 18.3 9 84 10.7 1.87 (0.77, 4.54) 1.32
Chen et al (2012) 720 2942 24.5 533 3762 14.2 1.96 (1.73, 2.22) 7.45
Chetty et al (2018) 214 2021 10.6 50 528 9.5 1.13 (0.82, 1.57) 4.85
Dryden-Peterson et al (2011) 59 258 22.9 32 170 18.8 1.28 (0.79, 2.07) 3.24
Lopez et al (2012) 67 298 22.5 35 221 15.8 1.54 (0.98, 2.42) 3.50
Moodley et al (2016) 573 2573 22.3 196 974 20.1 1.14 (0.95, 1.36) 6.74
Nlend et al (2016) 49 481 10.2 18 279 6.5 1.64 (0.94, 2.88) 2.67
Ramokolo et al (2017) 128 1101 11.6 84 646 13 0.88 (0.66, 1.18) 5.23
Schulte et al (2007) 461 2563 18 605 3665 16.5 1.11 (0.97, 1.27) 7.35
Sebitloane et al (2017) 192 725 26.5 99 417 23.7 1.16 (0.87, 1.53) 5.42
Short et al (2014) 38 251 15.1 4 72 5.6 3.03 (1.04, 8.81) 0.97
Sibiude et al (2012) 990 6738 14.7 474 4639 10.2 1.51 (1.35, 1.70) 7.53
Watts et al (2013) 310 1672 18.5 18 138 13 1.52 (0.91, 2.53) 3.02
Zash et al (2016) 1168 4392 26.6 598 2920 20.5 1.41 (1.26, 1.57) 7.58
Subtotal (I-squared = 79.4%, p = 0.000) 1.35 (1.17, 1.55) 66.87
Prospective
Chaudhury et al (2018) 29 382 7.6 26 210 12.4 0.58 (0.33, 1.02) 2.69
Darak et al (2013) 45 178 25.3 40 317 12.6 2.34 (1.46, 3.76) 3.31
Feiterna-Sperling et al (2007) 98 137 71.5 53 84 63.1 1.47 (0.82, 2.62) 2.56
Kakkar et al (2015) 54 371 14.6 9 77 11.7 1.29 (0.61, 2.73) 1.73
Kesho Bora Study Group et al (2010) 11 111 9.9 12 125 9.6 1.04 (0.44, 2.45) 1.39
Kowalska et al (2003) 8 46 17.4 4 35 11.4 1.63 (0.45, 5.93) 0.69
Machado et al (2009) 41 304 13.5 39 383 10.2 1.38 (0.86, 2.19) 3.37
Rudin et al (2011) 99 409 24.2 30 147 20.4 1.25 (0.79, 1.97) 3.42
Szyld et al (2006) 50 587 8.5 7 94 7.4 1.16 (0.51, 2.63) 1.50
Townsend et al - ECS (2010) 284 1624 17.5 120 1062 11.3 1.66 (1.32, 2.09) 6.10
Townsend et al - NSHPC (2010) 611 4776 12.8 116 1158 10 1.32 (1.07, 1.63) 6.36
Subtotal (I-squared = 43.2%, p = 0.062) 1.36 (1.12, 1.64) 33.13
Overall (I-squared = 70.2%, p = 0.000) 1.35 (1.21, 1.51) 100.00
0.1
0.5
1
2
10
HAART reduces the risk of PTB
HAART increases the risk of PTB

B

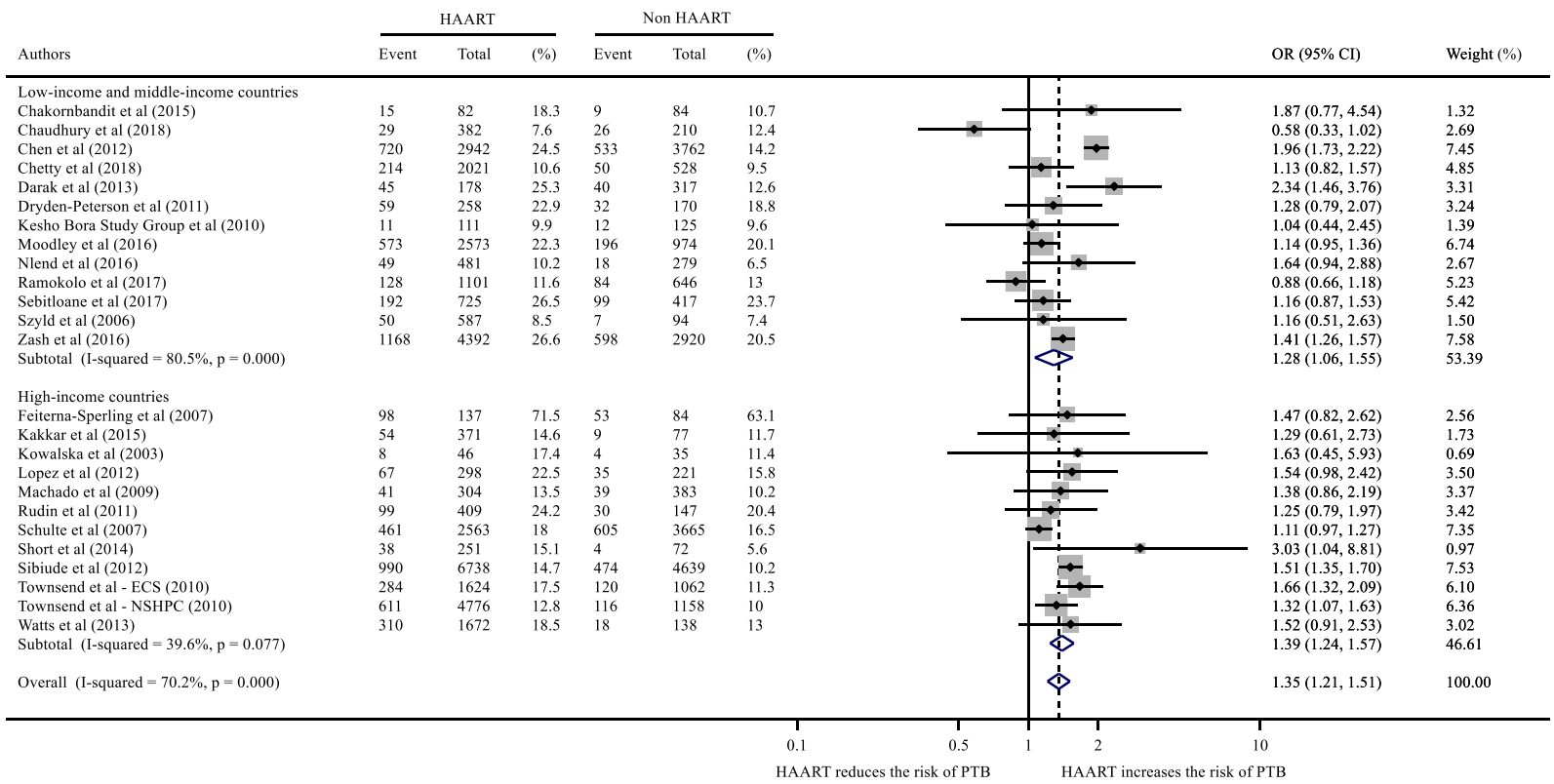


Figure 3.33. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

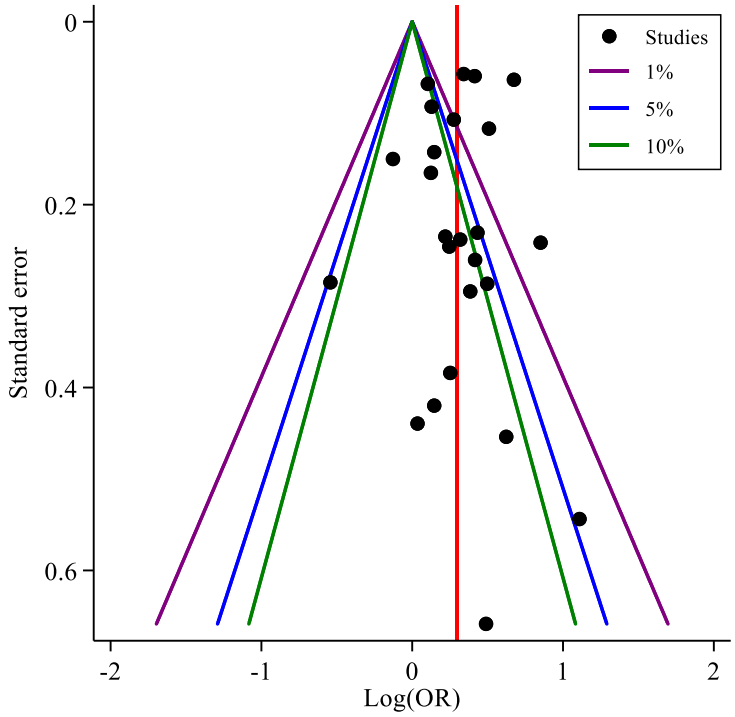


Figure 3.34. Contour-enhanced funnel plot of the 25 cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Solid black circles correspond to the 25 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Thirteen cohorts specified ART class: for non HAART, 11 used ZDV and two used ZDV and NRTIs dual therapy (all non HAART regimens were non PI); for HAART, five used both non PI and PI-based, six used non PI-based and two PI-based HAART only (Appendix 3.9: Figure 3.36 and Figure 3.37). Both non PI (pooled OR: 1.27, 95% CI: 1.01, 1.59) (Appendix 3.9: Figure 3.36) and PI-based HAART (pooled OR: 1.97, 95% CI: 1.55, 2.51) (Appendix 3.9: Figure 3.37) were associated with a higher risk of PTB compared with non HAART. Regarding timing of ART initiation, two cohorts included women starting ART pre-conception and post-conception, and 10 post-conception only (Appendix 3.9: Figure 3.38 and Figure 3.39). Among women starting ART pre-conception

(pooled OR: 6.28, 95% CI: 1.08, 36.57) (Appendix 3.9: Figure 3.38), HAART was associated with a higher risk of PTB compared with non HAART, and the association was also observed among women starting ART post-conception (pooled OR: 1.17, 95% CI: 1.01, 1.37) (Appendix 3.9: Figure 3.39).

The meta-analysis of adjusted effect estimates, including 12 cohorts, showed a higher risk of PTB in HIV-positive women on HAART than those on non HAART (pooled adjusted OR: 1.35, 95% CI: 1.11, 1.64), with moderate heterogeneity (I^2 = 70.8%) (Figure 3.35). The association persisted in the sub-group analysis of retrospective (pooled adjusted OR: 1.30, 95% CI: 1.03, 1.65), but not prospective cohorts (pooled adjusted OR: 1.53, 95% CI: 0.97, 2.39) (Figure 3.35A). The association also persisted in the sub-group analysis of cohorts in high-income countries (pooled adjusted OR: 1.49, 95% CI: 1.16, 1.91), but not in LMICs (pooled adjusted OR: 1.17, 95% CI: 0.80, 1.72) (Figure 3.35B). Several cohorts reported adjusted estimates for PTB risk in women on NRTI (n=1), NNRTI (n=4) and PI-based HAART (n=3) versus women on non HAART. PI-based HAART (pooled adjusted OR: 1.22, 95% CI: 1.06, 1.41), but not other HAART regimens, was associated with a higher risk of PTB compared with non HAART (Figure 3.36).

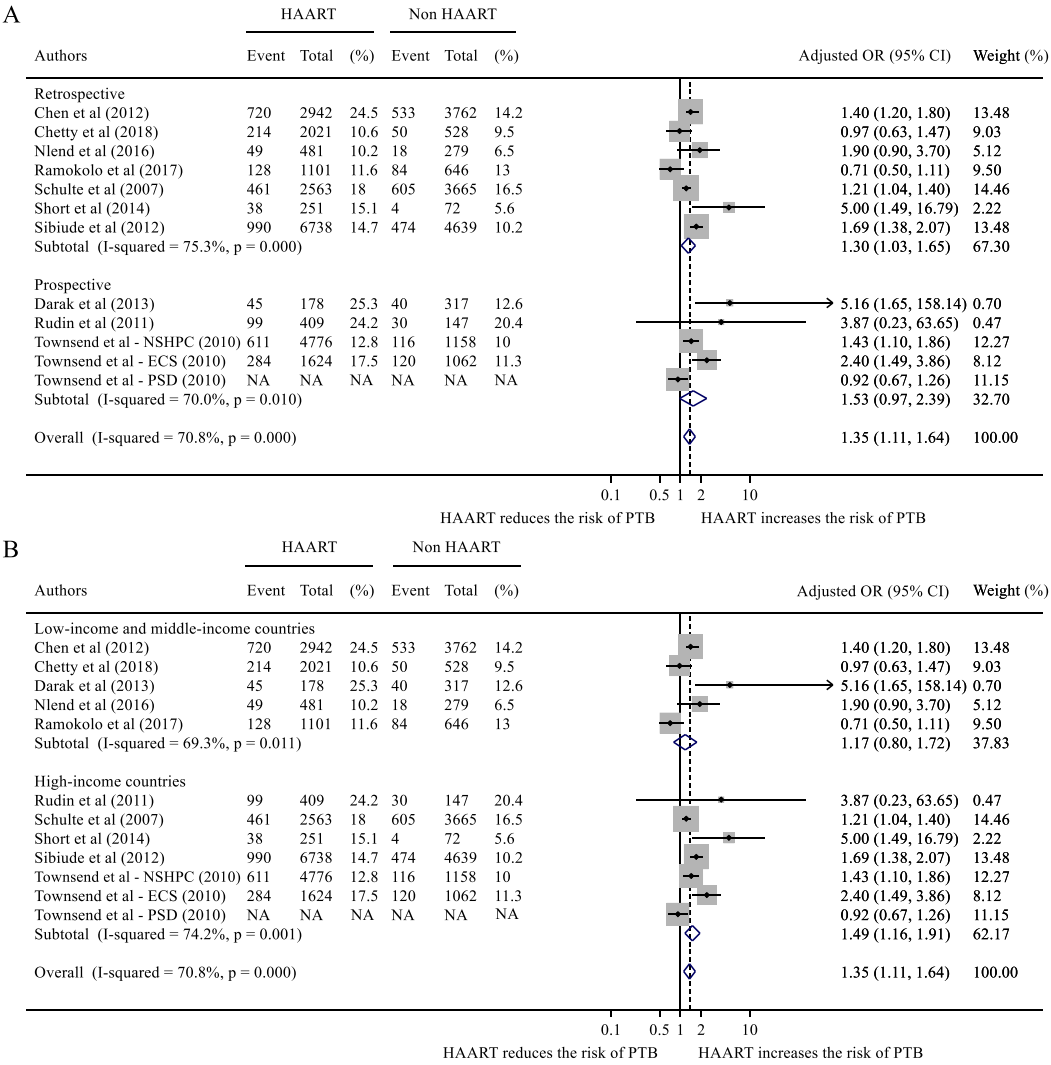


Figure 3.35. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using adjusted effect estimates, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; PTB, preterm birth.

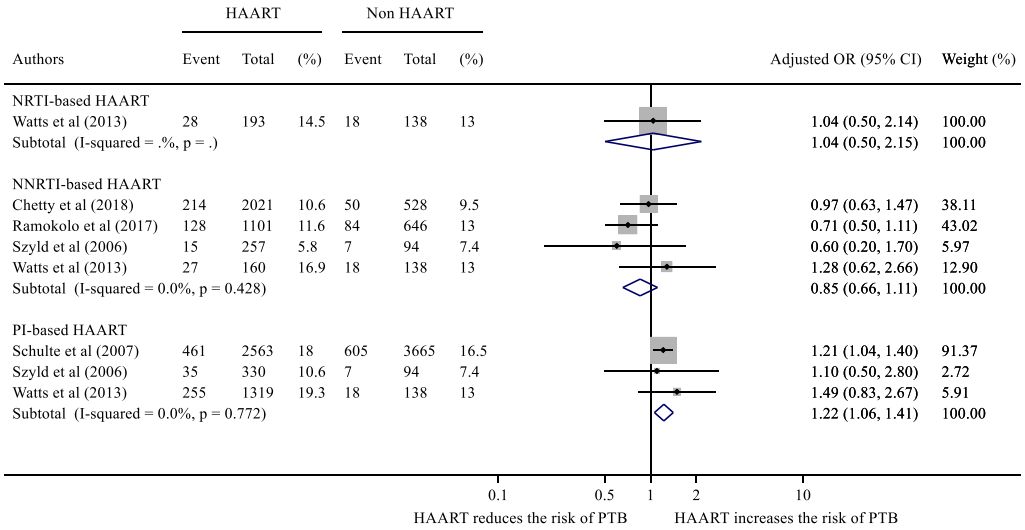


Figure 3.36. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with NRTI, NNRTI, or PI-based HAART versus non HAART using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

3.4.5.1.2 Spontaneous preterm birth (sPTB)

HAART versus non HAART

The pooled unadjusted effect estimates of three retrospective cohorts, including 2,495 women, showed no difference in sPTB risk between HAART and non HAART (pooled OR: 1.17, 95% CI: 0.81, 1.68) (Figure 3.37). Of these three cohorts, one reported adjusted effect estimates showing no differences in sPTB risk between non HAART and NRTI (adjusted OR: 0.88, 95% CI: 0.34, 2.29), NNRTI (adjusted OR: 1.53, 95% CI: 0.62, 3.81) and PI-based HAART (adjusted OR: 1.41, 95% CI: 0.66, 2.99) [372].

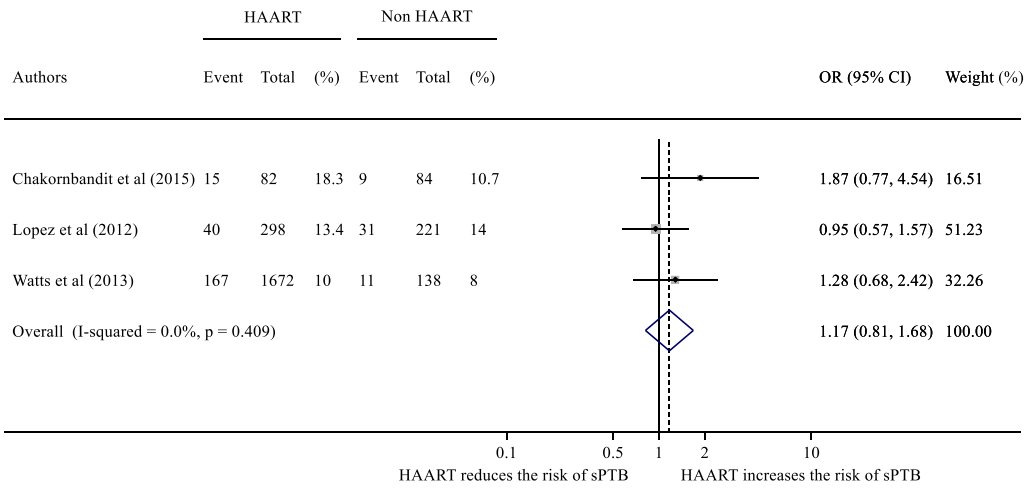


Figure 3.37. Forest plot of risk of spontaneous preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; sPTB, spontaneous preterm birth.

3.4.5.1.3 Very preterm birth (VPTB)

Combination therapy versus monotherapy

A retrospective cohort conducted in the USA, including 289 women, showed no association between combination therapy and VPTB compared with monotherapy (OR: 7.34, 95% CI: 0.41, 131.65) [369].

HAART versus non HAART

The meta-analysis of unajdusted effect estimates of two prospective cohorts conducted in high-income countries, including 5,001 women, showed no association between HAART and VPTB, compared with non HAART (pooled OR: 1.84, 95% CI: 0.74, 4.55) (Figure 3.38). Of these two cohorts, one reported an adjusted effect estimate showing a higher risk of VPTB in women receiving

HAART than in those receiving non HAART (adjusted OR: 2.63, 95% CI: 1.30, 5.33) [381].

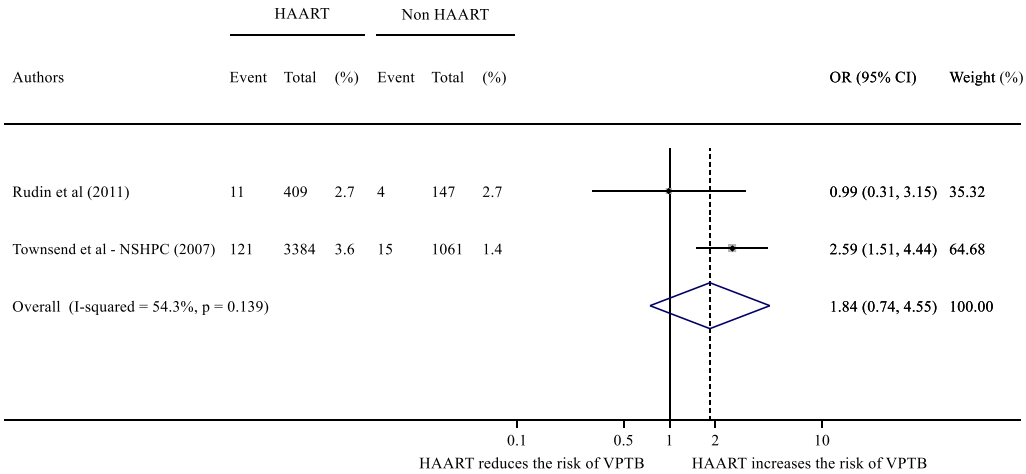


Figure 3.38. Forest plot of risk of very preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VPTB, very preterm birth.

3.4.5.2 Effect of ART complexity on birth weight

3.4.5.2.1 Low birth weight (LBW)

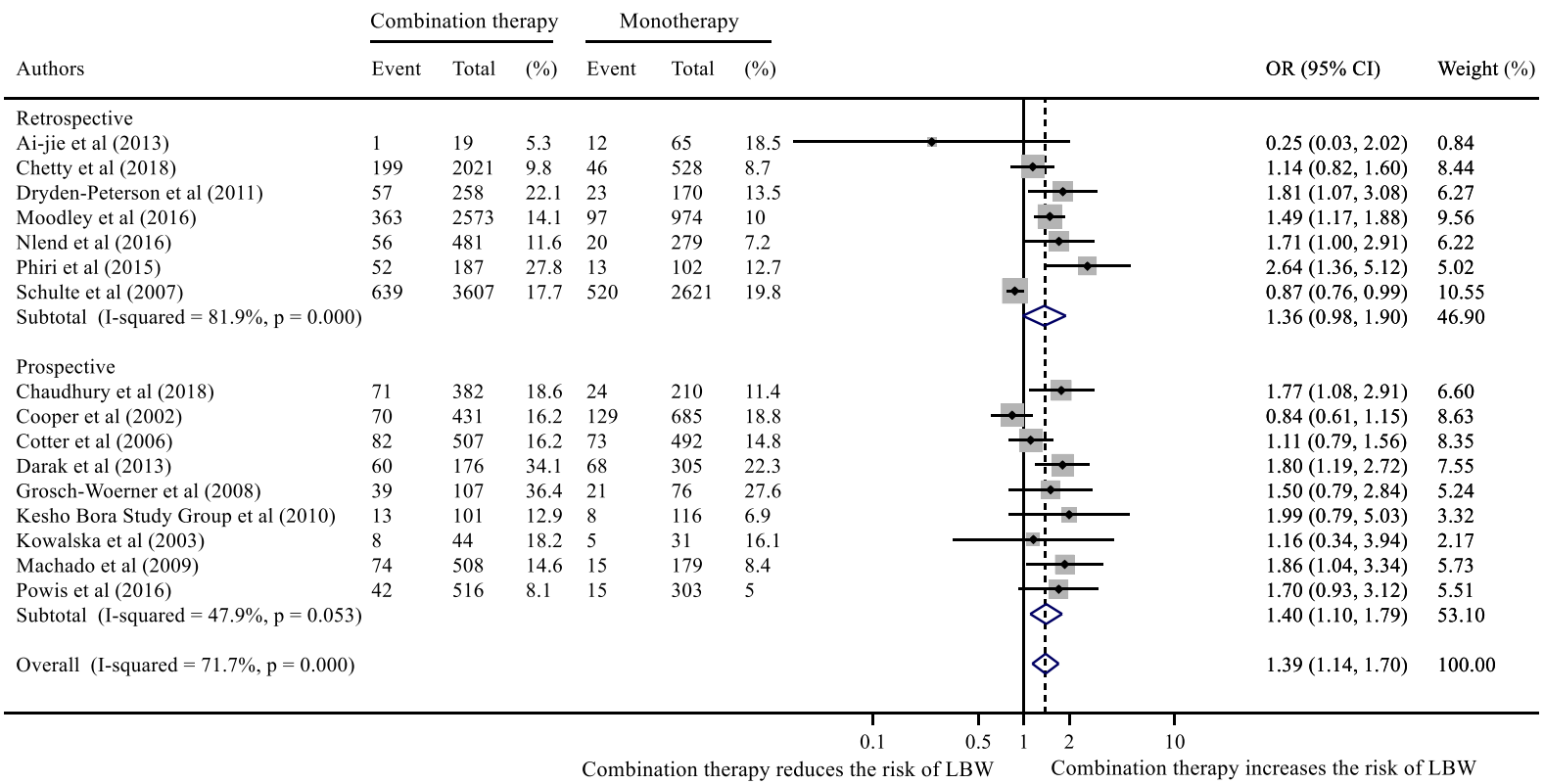
Combination therapy versus monotherapy

The risk of LBW in HIV-positive women on combination therapy versus those on monotherapy was reported in 16 cohorts (seven retrospective and nine prospective), including 19,054 women; nine cohorts were conducted in LMICs and seven in high-income countries (Figure 3.39). The synthesis of unadjusted effect estimates showed that combination therapy was associated with a higher risk of LBW than monotherapy (pooled OR: 1.39, 95% CI: 1.14, 1.70), with moderate heterogeneity (I^2 = 71.7%) (Figure 3.39). The association remained in

the sub-group analysis of prospective (pooled OR: 1.40, 95% CI: 1.10, 1.79), but not retrospective cohorts (pooled OR: 1.36, 95% CI: 0.98, 1.90). A high degree of heterogeneity was evident in retrospective (I^2 = 81.9%), but low heterogeneity in prospective cohorts (I^2 = 47.9%) (Figure 3.39A). The association remained in the sub-group analysis of cohorts in LMICs (pooled OR: 1.52, 95% CI: 1.31, 1.75), but not in high-income countries (pooled OR: 1.20, 95% CI: 0.90, 1.59). No heterogeneity was evident in LMIC (I^2 = 0%), but a moderate heterogeneity in high-income country (I^2 = 69.2%) (Figure 3.39B).

The contour-enhanced funnel plot in Figure 3.40 is rather asymmetric, and shows that: 1) smaller studies (standard error >0.2) tended to give results emphasising the effect of combination therapy on increasing LBW risk, and the majority of these studies showed a *P* value <0.05; 2) the hypothetical missing (smaller) studies appear to fall not only in the areas of statistical significance but also in areas of statistical non-significance. These data suggest that the observed asymmetric funnel plot is likely caused by several factors, not exclusively by publication bias. The Harbord's test showed a *P* value of 0.017, suggesting evidence of small-study effects.

A


Combination therapy
Monotherapy
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Ai-jie et al (2013) 1 19 5.3 12 65 18.5 0.25 (0.03, 2.02) 0.84
Chetty et al (2018) 199 2021 9.8 46 528 8.7 1.14 (0.82, 1.60) 8.44
Dryden-Peterson et al (2011) 57 258 22.1 23 170 13.5 1.81 (1.07, 3.08) 6.27
Moodley et al (2016) 363 2573 14.1 97 974 10 1.49 (1.17, 1.88) 9.56
Nlend et al (2016) 56 481 11.6 20 279 7.2 1.71 (1.00, 2.91) 6.22
Phiri et al (2015) 52 187 27.8 13 102 12.7 2.64 (1.36, 5.12) 5.02
Schulte et al (2007) 639 3607 17.7 520 2621 19.8 0.87 (0.76, 0.99) 10.55
Subtotal (I-squared = 81.9%, p = 0.000) 1.36 (0.98, 1.90) 46.90
Prospective
Chaudhury et al (2018) 71 382 18.6 24 210 11.4 1.77 (1.08, 2.91) 6.60
Cooper et al (2002) 70 431 16.2 129 685 18.8 0.84 (0.61, 1.15) 8.63
Cotter et al (2006) 82 507 16.2 73 492 14.8 1.11 (0.79, 1.56) 8.35
Darak et al (2013) 60 176 34.1 68 305 22.3 1.80 (1.19, 2.72) 7.55
Grosch-Woerner et al (2008) 39 107 36.4 21 76 27.6 1.50 (0.79, 2.84) 5.24
Kesho Bora Study Group et al (2010) 13 101 12.9 8 116 6.9 1.99 (0.79, 5.03) 3.32
Kowalska et al (2003) 8 44 18.2 5 31 16.1 1.16 (0.34, 3.94) 2.17
Machado et al (2009) 74 508 14.6 15 179 8.4 1.86 (1.04, 3.34) 5.73
Powis et al (2016) 42 516 8.1 15 303 5 1.70 (0.93, 3.12) 5.51
Subtotal (I-squared = 47.9%, p = 0.053) 1.40 (1.10, 1.79) 53.10
Overall (I-squared = 71.7%, p = 0.000) 1.39 (1.14, 1.70) 100.00
0.1
0.5
1
2
10
Combination therapy reduces the risk of LBW
Combination therapy increases the risk of LBW

B

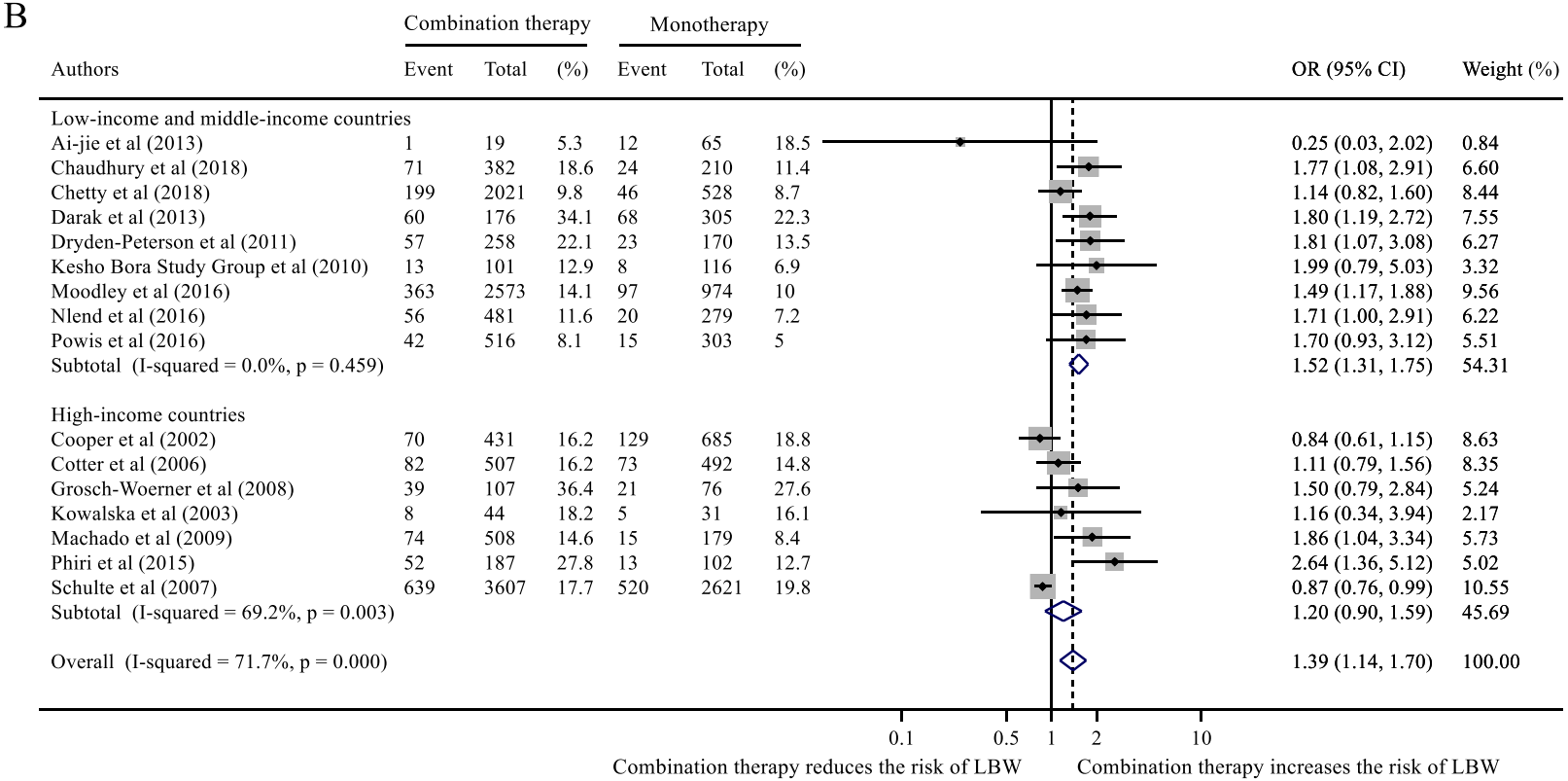


Figure 3.39. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

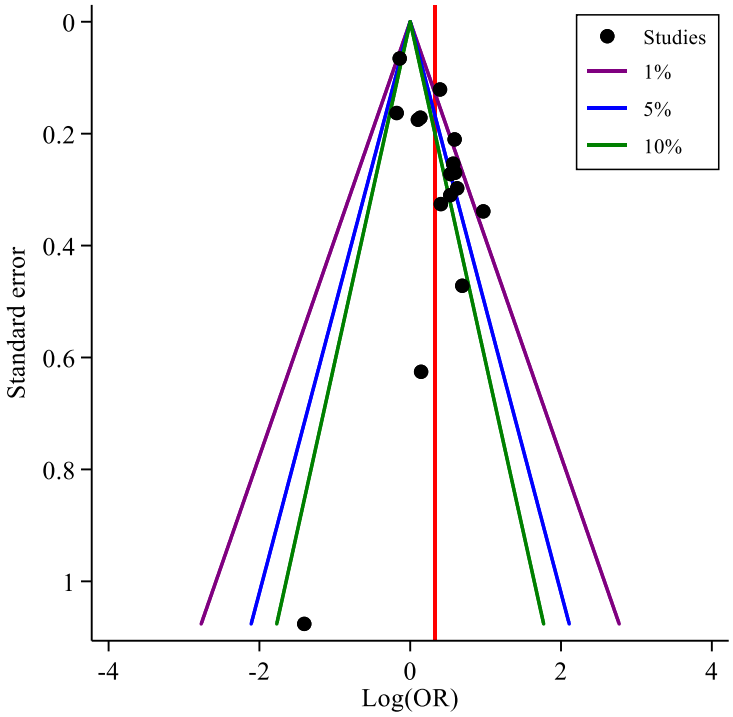


Figure 3.40. Contour-enhanced funnel plot of the 16 cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data. Solid black circles correspond to the 16 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The exploration of publication bias was then performed by cohort design and country-income status. The contour-enhanced funnel plot of prospective, but not retrospective cohorts, seems asymmetric with the hypothetical missing studies appearing to fall in the regions of both statistical significance and non-significance. The Harbord's tests showed *P* values of 0.207 and 0.146 for retrospective and prospective cohorts respectively, suggesting no evidence of small-study effects (Appendix 3.9: Figure 3.40). The contour-enhanced funnel plot of high-income country, but not LMIC, seems asymmetric with the hypothetical missing studies appearing to fall in the regions of both statistical

significance and non-significance. The Harbord's test showed evidence of small-study effects in high-income country (P = 0.047), but not LMIC (P = 0.964) (Appendix 3.9: Figure 3.41). However, these findings should be interpreted cautiously because there were few studies (<10) in each sub-group (Appendix 3.9: Figure 3.40 and Figure 3.41).

Eight cohorts specified ART class: for monotherapy, all cohorts used ZDV; for combination therapy, three used both non PI and PI-based and five non PI-based combination therapy only (Appendix 3.9: Figure 3.42 and Figure 3.43). Non PI (pooled OR: 1.39, 95% CI: 1.10, 1.76) (Appendix 3.9: Figure 3.42), but not PI-based combination therapy (pooled OR: 1.46, 95% CI: 0.99, 2.15) (Appendix 3.9: Figure 3.43), was associated with a higher risk of LBW than monotherapy.

Five cohorts (three retrospective and two prospective) reported adjusted effect estimates; four cohorts were conducted in LMICs and one in a high-income country. The pooled adjusted effect estimates showed a higher risk of LBW in HIV-positive women receiving combination therapy than in those receiving monotherapy (pooled adjusted OR: 1.29, 95% CI: 1.02, 1.63), with no heterogeneity (I^2 = 4.5%) (Figure 3.41). The finding persisted in the sub-group analysis of retrospective (pooled adjusted OR: 1.35, 95% CI: 1.06, 1.71), but not prospective cohorts (pooled adjusted OR: 1.00, 95% CI: 0.43, 2.31) (Figure 3.41).

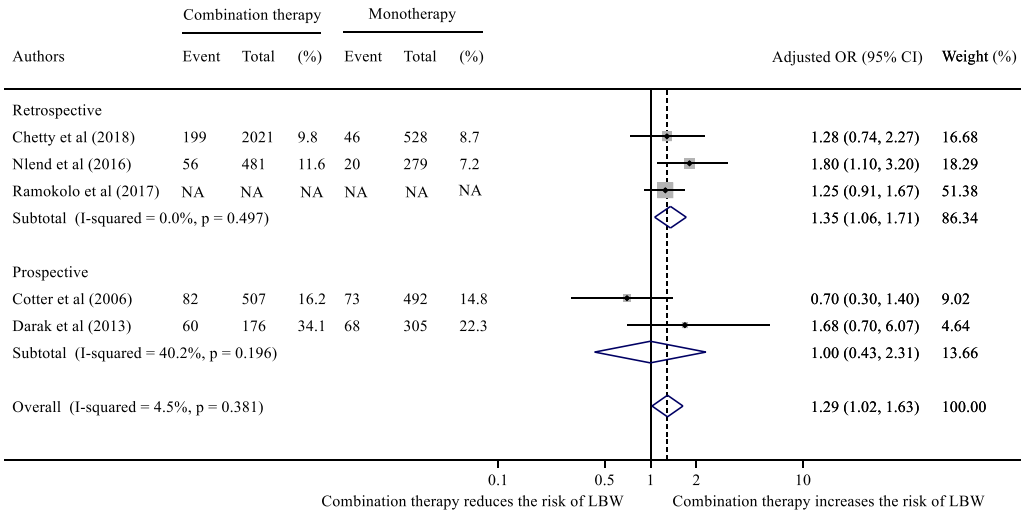


Figure 3.41. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using adjusted effect estimates, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; NA, not available; OR, odds ratio.

Dual therapy versus monotherapy

The pooled unadjusted effect estimates of five cohorts (two retrospective and three prospective) conducted in high-income countries, including 5,205 women, showed no association between dual therapy and LBW compared with monotherapy (pooled OR: 1.32, 95% CI: 0.80, 2.17), with a high degree of heterogeneity (I^2 = 79.3%) (Figure 3.42). The finding persisted across cohort design: retrospective (pooled OR: 1.60, 95% CI: 0.39, 6.46) and prospective (pooled OR: 1.22, 95% CI: 0.67, 2.23) (Figure 3.42).

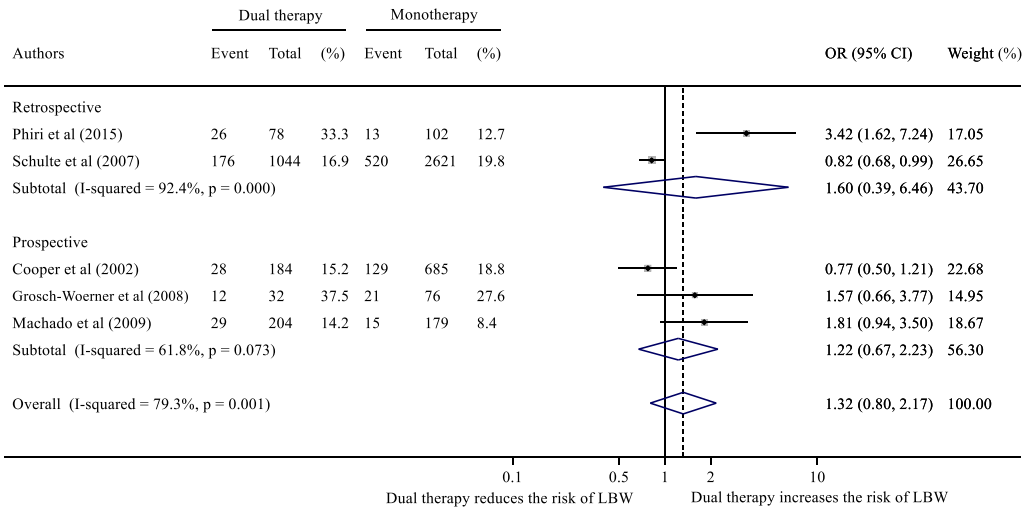


Figure 3.42. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with dual therapy versus monotherapy using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

HAART versus monotherapy

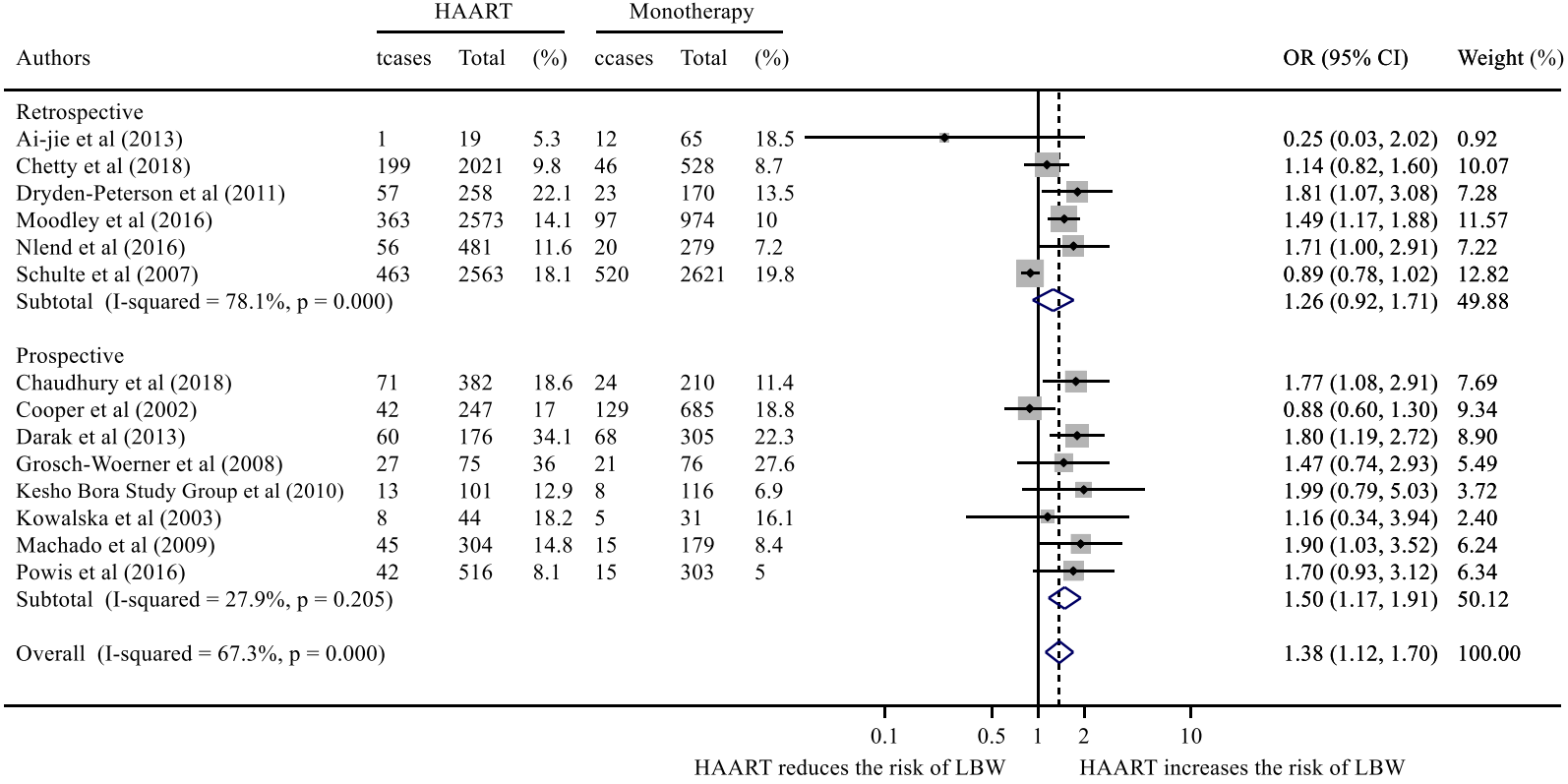
The risk of LBW in HIV-positive women on HAART versus women on monotherapy was reported in 14 cohorts (six retrospective and eight prospective), including 16,302 women; nine cohorts were conducted in LMICs and five in high-income countries (Figure 3.43). The synthesis of unadjusted effect estimates showed that HAART was associated with a higher risk of LBW compared with monotherapy (pooled OR: 1.38, 95% CI: 1.12, 1.70); moderate heterogeneity (I^2 = 67.3%) was evident (Figure 3.43). The association remained in the sub-group analysis of prospective (pooled OR: 1.50, 95% CI: 1.17, 1.91), but not retrospective cohorts (pooled OR: 1.26, 95% CI: 0.92, 1.71) (Figure 3.43A). A high degree of heterogeneity was observed in retrospective (I^2 = 78.1%), but low heterogeneity in prospective cohorts (I^2 = 27.9%) (Figure 3.43A). HAART remained associated with a higher risk of LBW in the sub-group analysis of

cohorts in LMICs (pooled OR: 1.52, 95% CI: 1.31, 1.75), but not in high-income countries (pooled OR: 1.07, 95% CI: 0.81, 1.41) (Figure 3.43B). No heterogeneity was observed in LMIC (I^2 = 0%), but low heterogeneity in high-income country (I^2 = 46.1%) (Figure 3.43B).

Figure 3.44 shows an asymmetric contour-enhanced funnel plot; the Harbord's test had a *P* value of 0.059. This funnel plot should be interpreted similarly to that for "combination therapy versus monotherapy" for the risk of LBW (Figure 3.40). The same applies to the contour-enhanced funnel plots by cohort design (Appendix 3.9: Figure 3.44) and country-income status (Appendix 3.9: Figure 3.45), i.e. they are similar to those for "combination therapy versus monotherapy" for the risk of LBW (Appendix 3.9: Figure 3.40 and Figure 3.41).

Six cohorts specified ART class: for monotherapy, all cohorts used ZDV; for HAART, two used both non PI and PI-based, and four non PI-based HAART only (Appendix 3.9: Figure 3.46 and Figure 3.47). Both non PI (pooled OR: 1.36, 95% CI: 1.12, 1.66) (Appendix 3.9: Figure 3.46) and PI-based HAART (pooled OR: 1.91, 95% CI: 1.06, 3.45) (Appendix 3.9: Figure 3.47) were associated with a higher risk of LBW compared with monotherapy.

A


HAART
Monotherapy
Authors
tcases Total (%) ccases Total (%)
OR (95% CI) Weight (%)
Retrospective
Ai-jie et al (2013) 1 19 5.3 12 65 18.5 0.25 (0.03, 2.02) 0.92
Chetty et al (2018) 199 2021 9.8 46 528 8.7 1.14 (0.82, 1.60) 10.07
Dryden-Peterson et al (2011) 57 258 22.1 23 170 13.5 1.81 (1.07, 3.08) 7.28
Moodley et al (2016) 363 2573 14.1 97 974 10 1.49 (1.17, 1.88) 11.57
Nlend et al (2016) 56 481 11.6 20 279 7.2 1.71 (1.00, 2.91) 7.22
Schulte et al (2007) 463 2563 18.1 520 2621 19.8 0.89 (0.78, 1.02) 12.82
Subtotal (I-squared = 78.1%, p = 0.000) 1.26 (0.92, 1.71) 49.88
Prospective
Chaudhury et al (2018) 71 382 18.6 24 210 11.4 1.77 (1.08, 2.91) 7.69
Cooper et al (2002) 42 247 17 129 685 18.8 0.88 (0.60, 1.30) 9.34
Darak et al (2013) 60 176 34.1 68 305 22.3 1.80 (1.19, 2.72) 8.90
Grosch-Woerner et al (2008) 27 75 36 21 76 27.6 1.47 (0.74, 2.93) 5.49
Kesho Bora Study Group et al (2010) 13 101 12.9 8 116 6.9 1.99 (0.79, 5.03) 3.72
Kowalska et al (2003) 8 44 18.2 5 31 16.1 1.16 (0.34, 3.94) 2.40
Machado et al (2009) 45 304 14.8 15 179 8.4 1.90 (1.03, 3.52) 6.24
Powis et al (2016) 42 516 8.1 15 303 5 1.70 (0.93, 3.12) 6.34
Subtotal (I-squared = 27.9%, p = 0.205) 1.50 (1.17, 1.91) 50.12
Overall (I-squared = 67.3%, p = 0.000) 1.38 (1.12, 1.70) 100.00
0.1 0.5 1 2 10
HAART reduces the risk of LBW
HAART increases the risk of LBW

B

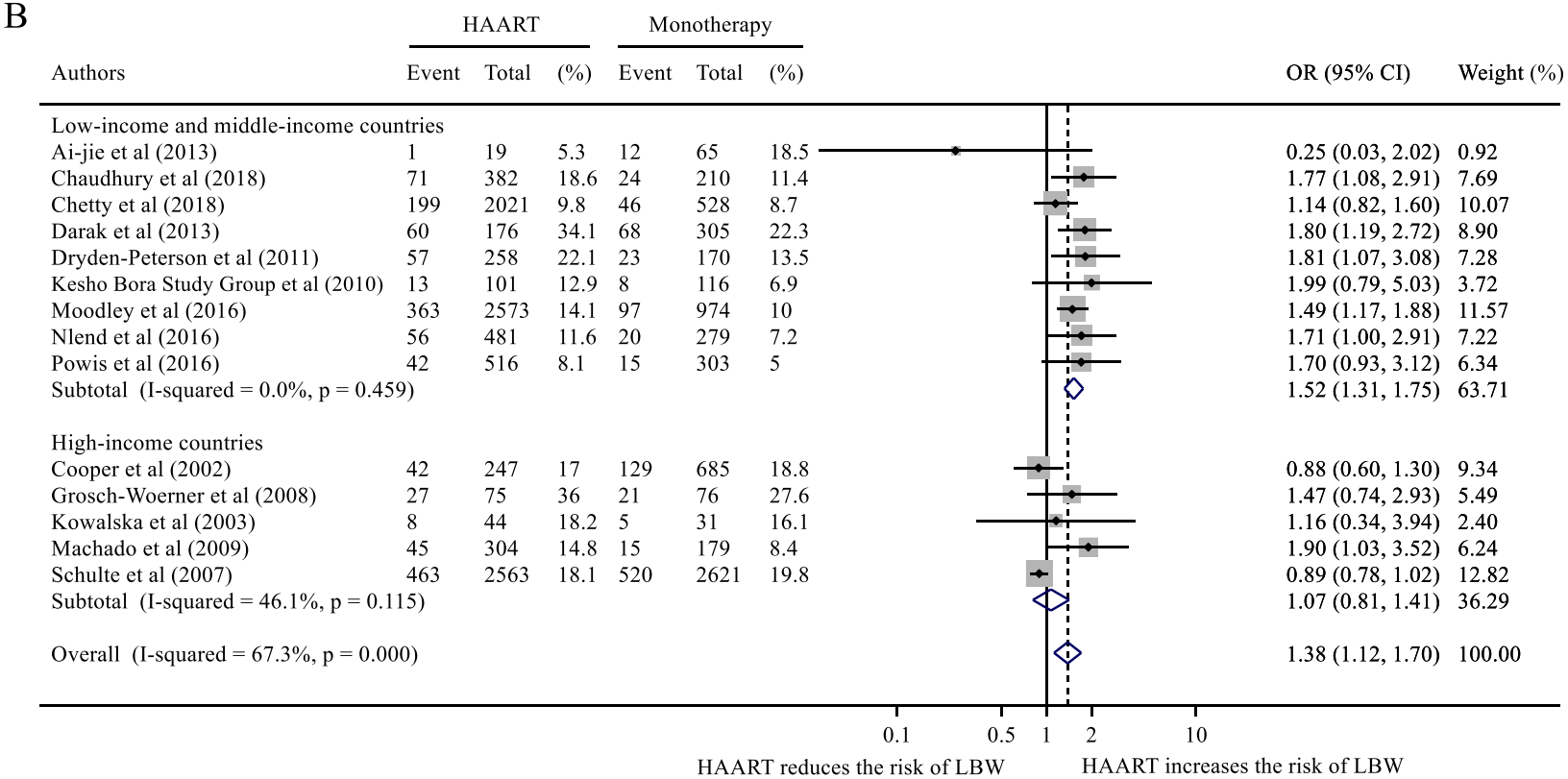


Figure 3.43. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

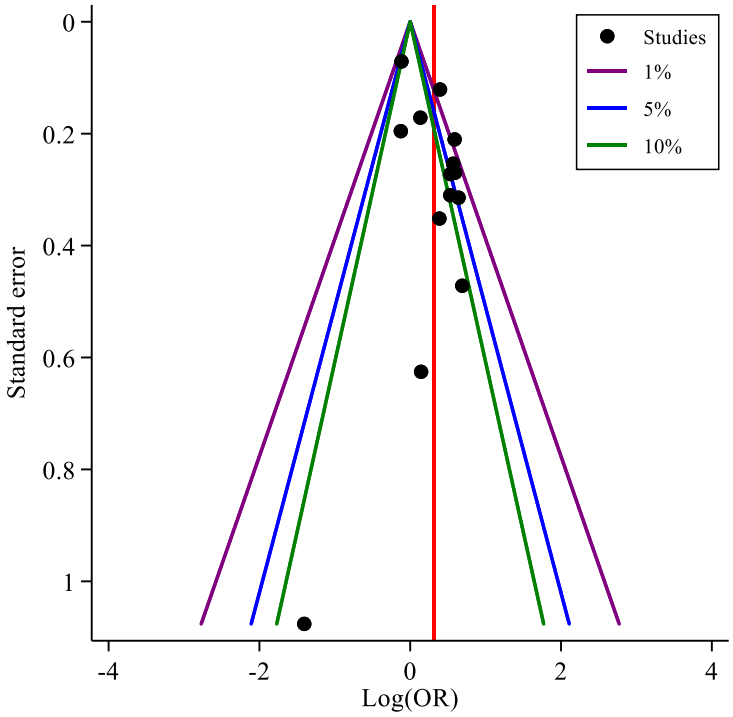


Figure 3.44. Contour-enhanced funnel plot of the 14 cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data. Solid black circles correspond to the 14 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The meta-analysis of adjusted effect estimates of four cohorts (three retrospective and one prospective) conducted in LMICs showed that HAART was associated with a higher risk of LBW than monotherapy (pooled adjusted OR: 1.36, 95% CI: 1.08, 1.72), with no heterogeneity (I^2 = 0%) (Figure 3.45).

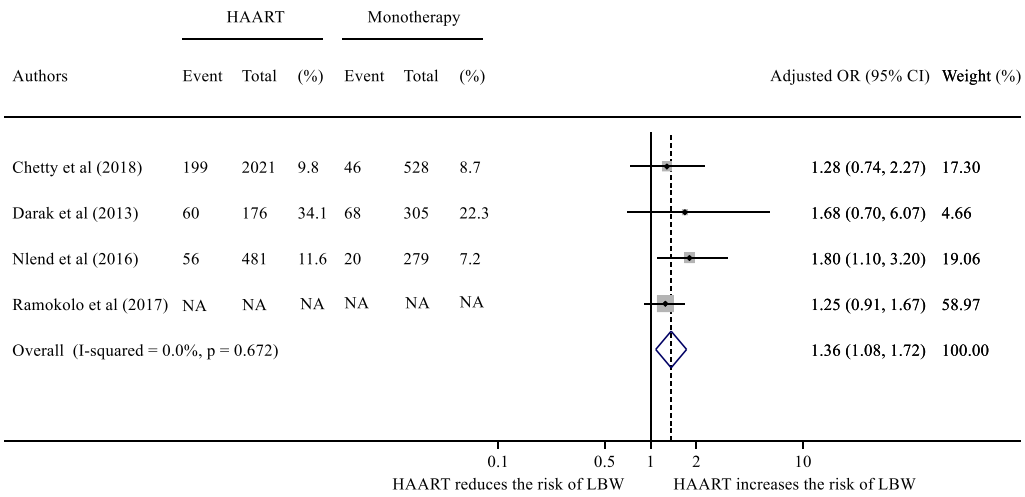


Figure 3.45. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with HAART versus monotherapy using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; NA, not available; OR, odds ratio.

HAART versus dual therapy

The pooled unadjusted effect estimates of four cohorts (one retrospective and three prospective) conducted in high-income countries, including 4,653 women, showed no association between HAART and LBW compared with dual therapy (pooled OR: 1.08, 95% CI: 0.92, 1.28); no heterogeneity (I^2 = 0%) was observed (Figure 3.46).

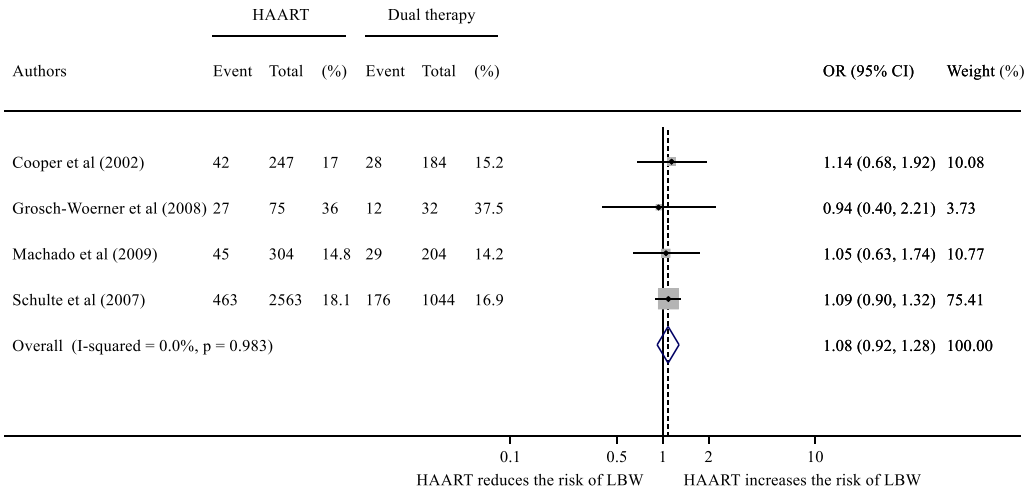


Figure 3.46. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with HAART versus dual therapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

HAART versus non HAART

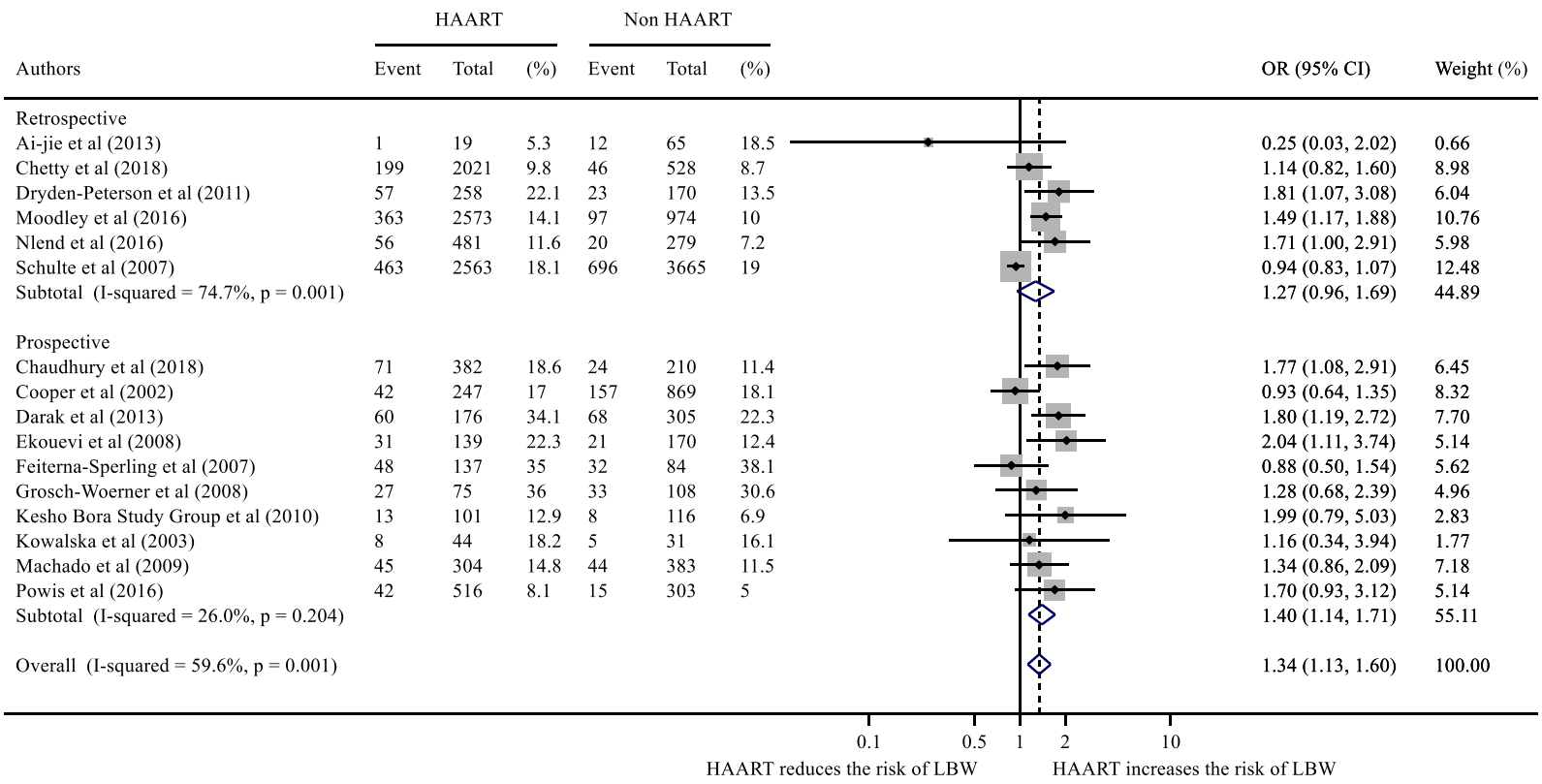
The risk of LBW in HIV-positive pregnant women receiving HAART versus those receiving non HAART was reported in 16 cohorts (six retrospective and 10 prospective), including 18,296 women; 10 cohorts in LMICs and six in high-income countries (Figure 3.47). The pooled unadjusted effect estimates showed that HAART was associated with a higher risk of LBW compared with non HAART (pooled OR: 1.34, 95% CI: 1.13, 1.60); moderate heterogeneity (I^2 = 59.6%) was observed (Figure 3.47). The association persisted in the sub-group analysis of prospective (pooled OR: 1.40, 95% CI: 1.14, 1.71), but not retrospective cohorts (pooled OR: 1.27, 95% CI: 0.96, 1.69); a high degree of heterogeneity (I^2 = 75%) was observed in retrospective, but low heterogeneity in prospective cohorts (I^2 = 26%) (Figure 3.47A). The association persisted in the

sub-group analysis of cohorts in LMICs (pooled OR: 1.54, 95% CI: 1.34, 1.78), but not in high-income countries (pooled OR: 0.97, 95% CI: 0.87, 1.09); no heterogeneity (I^2 = 0%) was observed in either sub-group (Figure 3.47B).

Figure 3.48 shows a symmetric contour-enhanced funnel plot, indicating no evidence of publication bias; the Harbord's test had a *P* value of 0.265, indicating no evidence of small-study effects.

Seven cohorts specified ART class: for non HAART, five cohorts used ZDV, and two ZDV and NRTIs dual therapy; for HAART, two used both non PI and PI-based, and five non PI-based HAART only (Appendix 3.9: Figure 3.48). Non PI (pooled OR: 1.38, 95% CI: 1.12, 1.70) (Appendix 3.9: Figure 3.48A), but not PI-based HAART (pooled OR: 1.42, 95% CI: 0.89, 2.25) (Appendix 3.9: Figure 3.48B), was associated with a higher risk of LBW compared with non HAART.

A


HAART
Non HAART
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Ai-jie et al (2013) 1 19 5.3 12 65 18.5 0.25 (0.03, 2.02) 0.66
Chetty et al (2018) 199 2021 9.8 46 528 8.7 1.14 (0.82, 1.60) 8.98
Dryden-Peterson et al (2011) 57 258 22.1 23 170 13.5 1.81 (1.07, 3.08) 6.04
Moodley et al (2016) 363 2573 14.1 97 974 10 1.49 (1.17, 1.88) 10.76
Nlend et al (2016) 56 481 11.6 20 279 7.2 1.71 (1.00, 2.91) 5.98
Schulte et al (2007) 463 2563 18.1 696 3665 19 0.94 (0.83, 1.07) 12.48
Subtotal (I-squared = 74.7%, p = 0.001) 1.27 (0.96, 1.69) 44.89
Prospective
Chaudhury et al (2018) 71 382 18.6 24 210 11.4 1.77 (1.08, 2.91) 6.45
Cooper et al (2002) 42 247 17 157 869 18.1 0.93 (0.64, 1.35) 8.32
Darak et al (2013) 60 176 34.1 68 305 22.3 1.80 (1.19, 2.72) 7.70
Ekouevi et al (2008) 31 139 22.3 21 170 12.4 2.04 (1.11, 3.74) 5.14
Feiterna-Sperling et al (2007) 48 137 35 32 84 38.1 0.88 (0.50, 1.54) 5.62
Grosch-Woerner et al (2008) 27 75 36 33 108 30.6 1.28 (0.68, 2.39) 4.96
Kesho Bora Study Group et al (2010) 13 101 12.9 8 116 6.9 1.99 (0.79, 5.03) 2.83
Kowalska et al (2003) 8 44 18.2 5 31 16.1 1.16 (0.34, 3.94) 1.77
Machado et al (2009) 45 304 14.8 44 383 11.5 1.34 (0.86, 2.09) 7.18
Powis et al (2016) 42 516 8.1 15 303 5 1.70 (0.93, 3.12) 5.14
Subtotal (I-squared = 26.0%, p = 0.204) 1.40 (1.14, 1.71) 55.11
Overall (I-squared = 59.6%, p = 0.001) 1.34 (1.13, 1.60) 100.00
0.1
0.5
1
2
10
HAART reduces the risk of LBW
HAART increases the risk of LBW

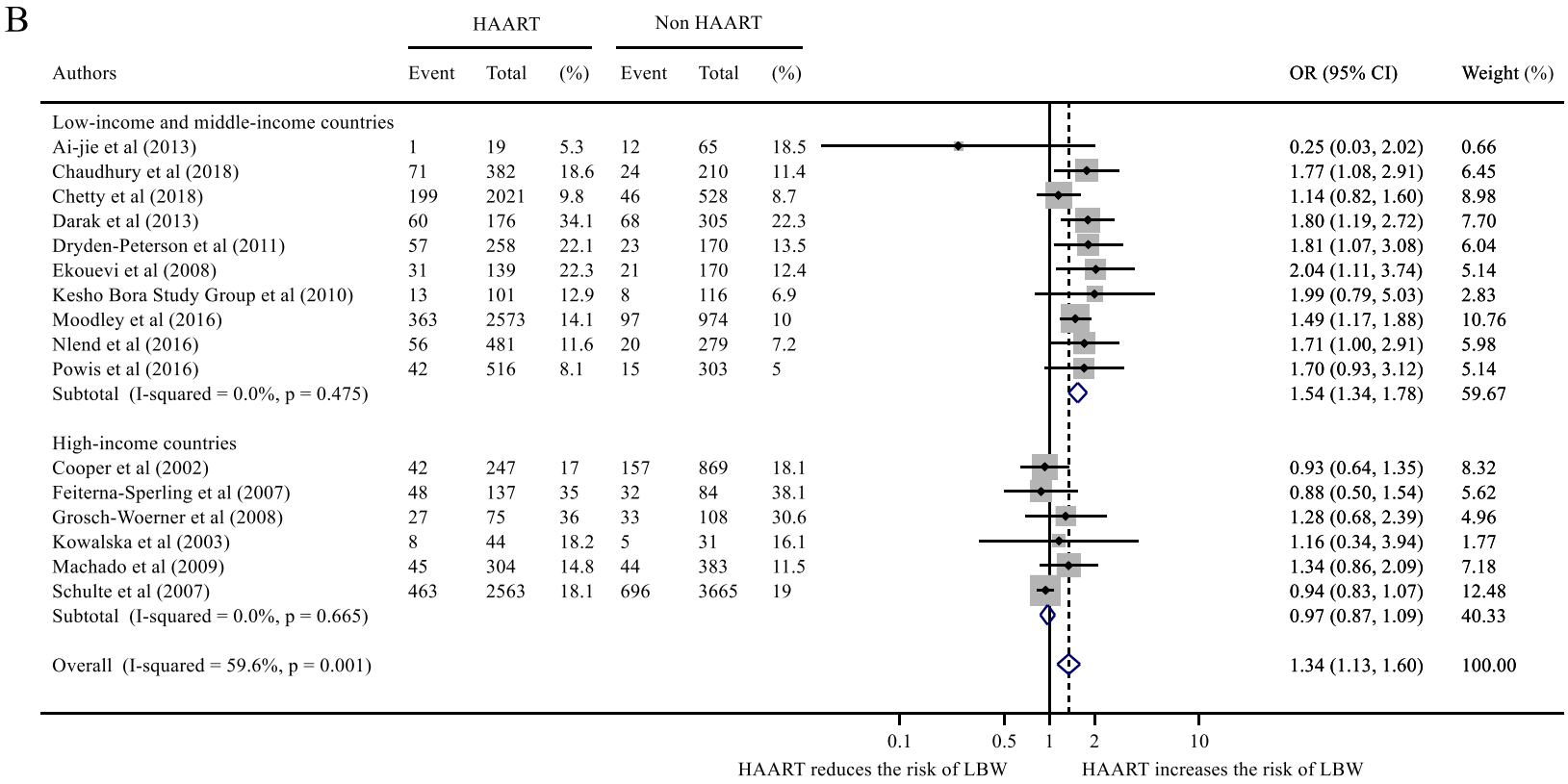


Figure 3.47. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

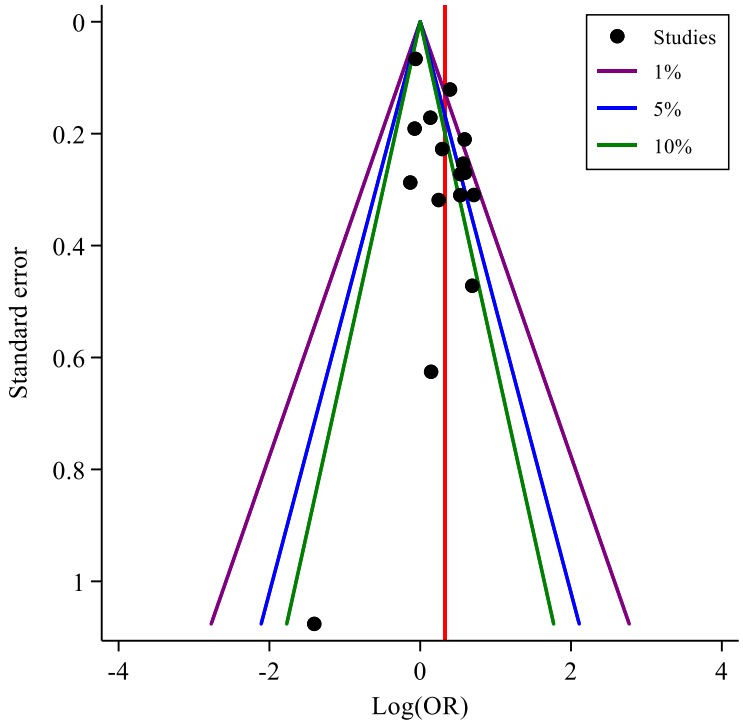


Figure 3.48. Contour-enhanced funnel plot of the 16 cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Solid black circles correspond to the 16 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The meta-analysis of adjusted effect estimates including five cohorts (three retrospective and two prospective) conducted in LMICs showed an association between HAART and an increased risk of LBW compared with non HAART (pooled adjusted OR: 1.42, 95% CI: 1.13, 1.78); no heterogeneity (I^2 = 0%) was observed. The association persisted across cohort design: retrospective (pooled adjusted OR: 1.35, 95% CI: 1.06, 1.71) and prospective (pooled adjusted OR: 2.27, 95% CI: 1.11, 4.65) (Figure 3.49).

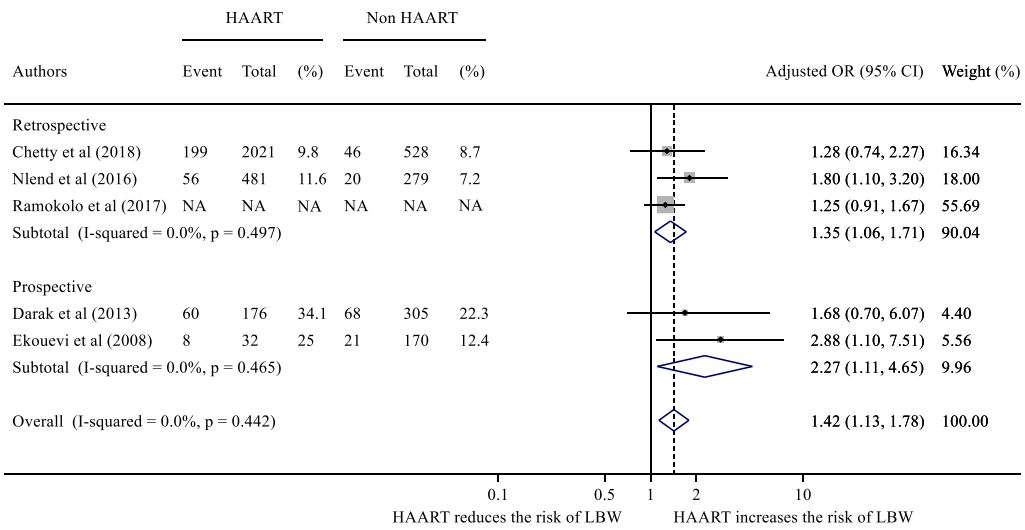


Figure 3.49. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with HAART versus non HAART using adjusted effect estimates, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

3.4.5.2.2 Very low birth weight (VLBW)

Combination therapy versus monotherapy

The pooled unadjusted effect estimates of two cohorts (one retrospective and one prospective) conducted in the USA, including 1,288 women, showed an increased risk of VLWB in HIV-positive women receiving combination therapy compared with those receiving monotherapy (pooled OR: 2.34, 95% CI: 1.11, 4.91) (Figure 3.50).

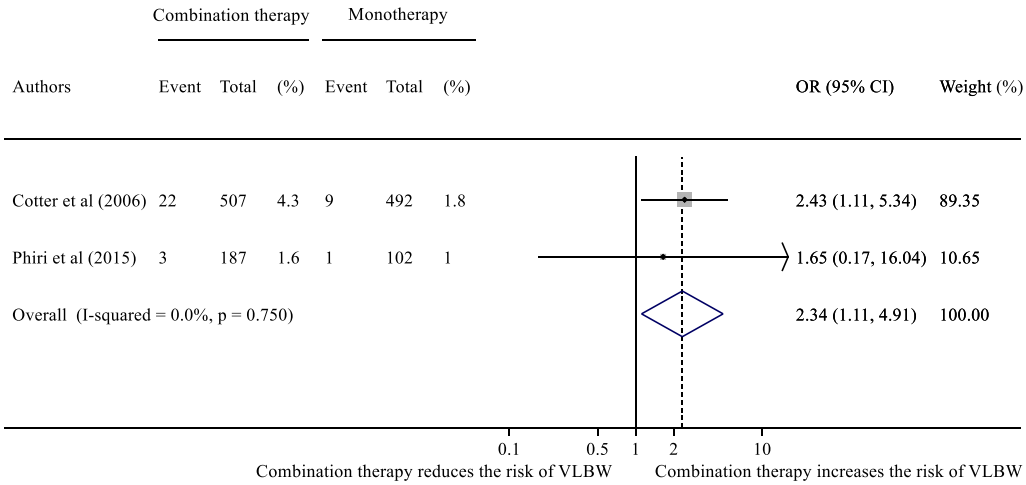


Figure 3.50. Forest plot of risk of very low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VLBW, very low birth weight.

3.4.5.3 Effect of ART complexity on gestational age and birth weight combined

3.4.5.3.1 Small for gestational age (SGA)

Combination therapy versus monotherapy

The risk of SGA in HIV-positive pregnant women treated with combination therapy versus monotherapy was reported in six retrospective cohorts, including 15,487 women; four were conducted in LMICs and two in high-income countries (Figure 3.51). The meta-analysis of unadjusted effect estimates revealed that combination therapy was associated with an increased risk of SGA compared with monotherapy (pooled OR: 1.14, 95% CI: 1.04, 1.25); no heterogeneity (I^2 = 0%) was evident (Figure 3.51). The association remained in the sub-group analysis of cohorts conducted in LMICs (pooled OR: 1.15, 95% CI: 1.03, 1.28), but not in high-income countries (pooled OR: 1.10, 95% CI: 0.81, 1.51) (Figure 3.51).

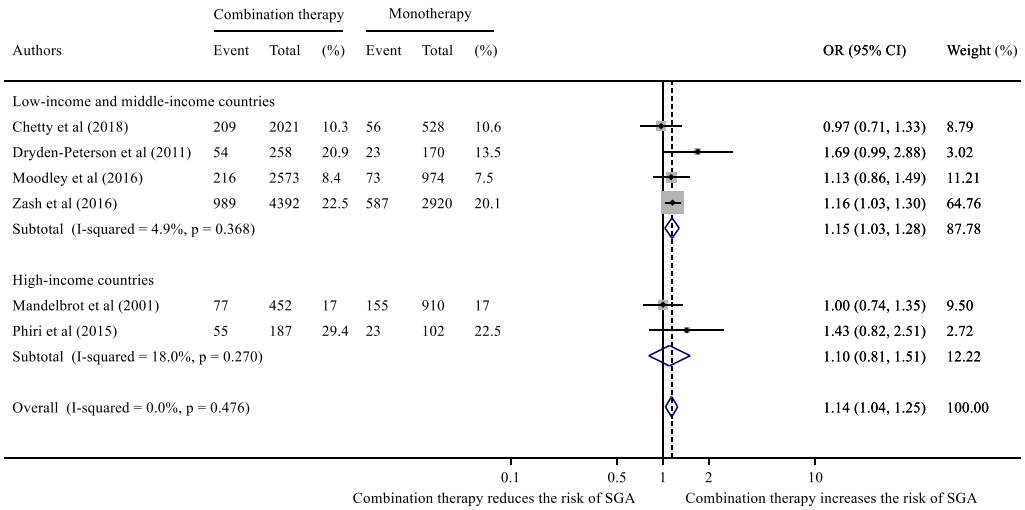


Figure 3.51. Forest plot of risk of small for gestational age in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

Dual therapy versus monotherapy

The pooled unadjusted effect estimates of two retrospective cohorts conducted in high-income countries, including 1,542 women, showed no difference in SGA risk between dual therapy and monotherapy (pooled OR: 1.30, 95% CI: 0.69, 2.43) (Figure 3.52).

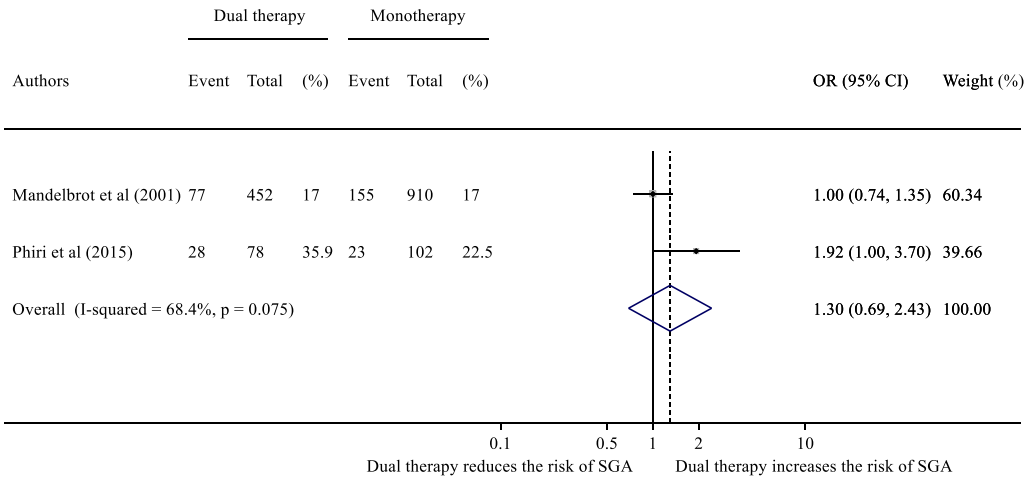


Figure 3.52. Forest plot of risk of small for gestational age in HIV-positive pregnant women treated with dual therapy versus monotherapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

HAART versus monotherapy

The risk of SGA in HIV-positive pregnant women treated with HAART versus monotherapy was reported in six retrospective cohorts conducted in LMICs. Of these, four provided the raw data, including 13,836 women: there was an increased risk of SGA among women on HAART compared with those on monotherapy (pooled OR: 1.15, 95% CI: 1.03, 1.28); no heterogeneity (I^2 = 4.9%) was observed (Figure 3.53A). The association persisted in the meta-analysis of adjusted effect estimates of three cohorts (pooled adjusted OR: 1.43, 95% CI: 1.19, 1.71) (Figure 3.53B).

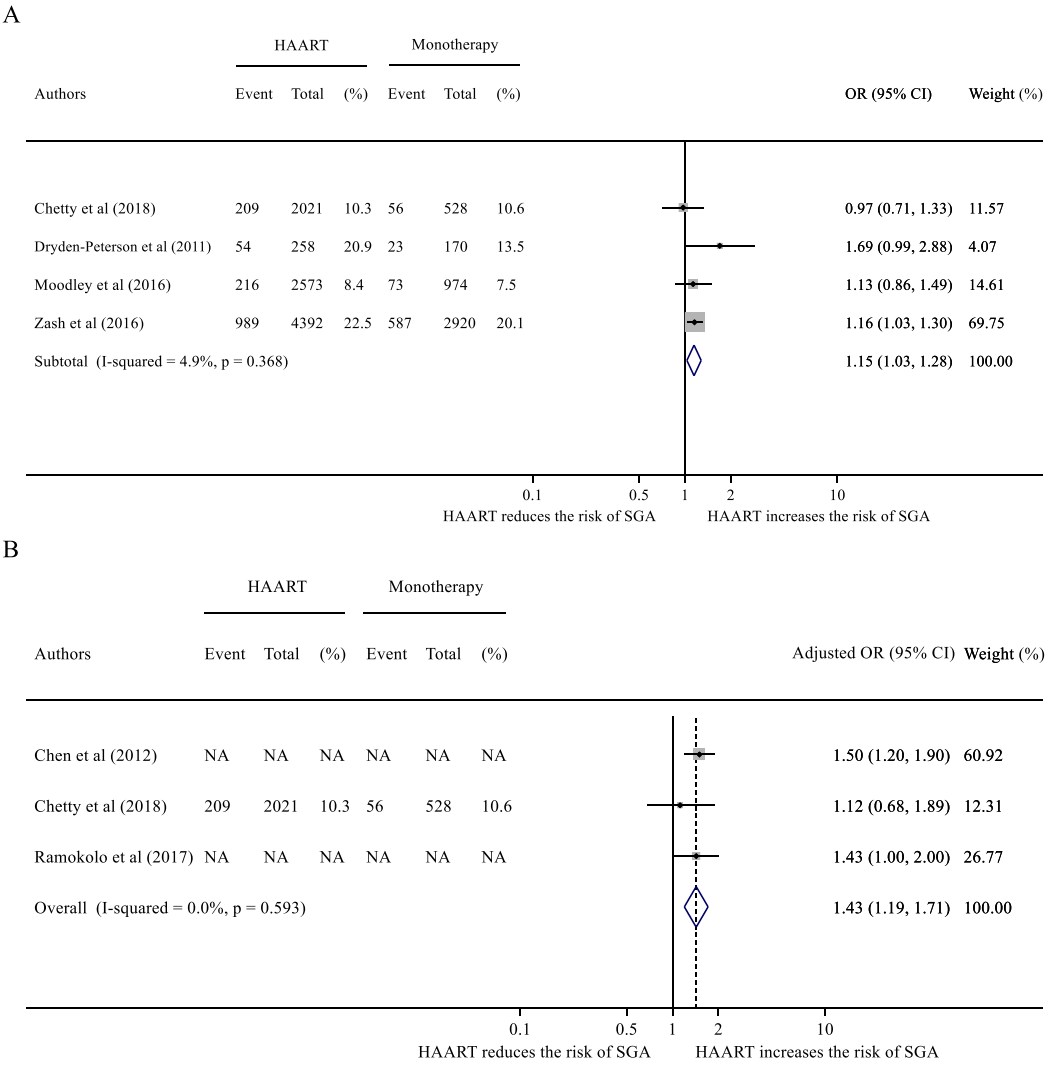


Figure 3.53. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted (A) and adjusted effect estimates (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; SGA, small for gestational age.

HAART versus non HAART

An increased risk of SGA in HIV-positive women receiving HAART compared with those receiving non HAART (pooled OR: 1.15, 95% CI: 1.04, 1.27) was shown by the meta-analysis of unadjusted effect estimates of five retrospective

cohorts, including 15,632 women. No heterogeneity (I^2 = 0%) was observed in this meta-analysis (Figure 3.54). Sub-group analysis by country-income status was not performed because, of these five retrospective cohorts, only one conducted in high-income countries [372].

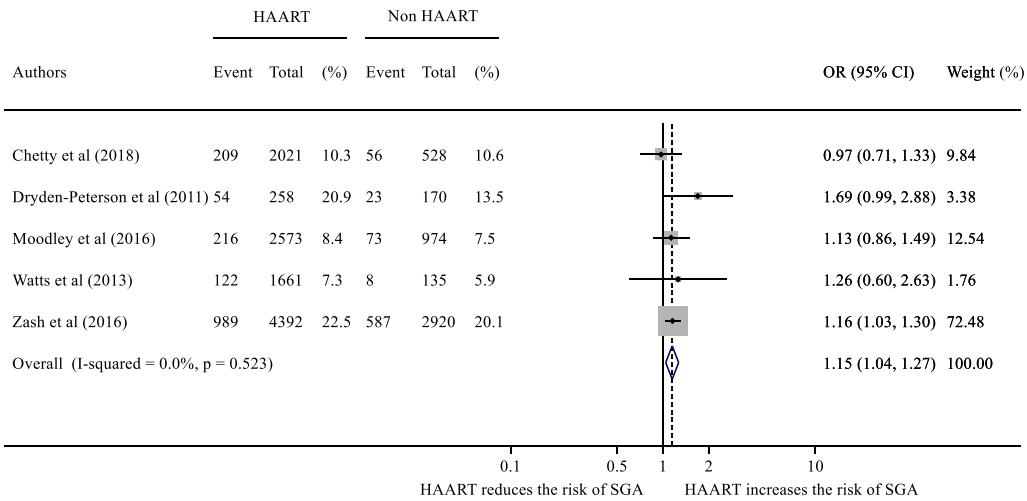


Figure 3.54. Forest plot of risk of small for gestational age in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

Several cohorts reported adjusted effect estimates for SGA risk in women on NRTI (n=1), NNRTI (n=3) and PI-based HAART (n=1) compared with those on non HAART. NNRTI-based HAART (pooled adjusted OR: 1.34, 95% CI: 1.02, 1.78), but not other HAART regimens, was associated with an increased risk of SGA compared with non HAART (Figure 3.55).

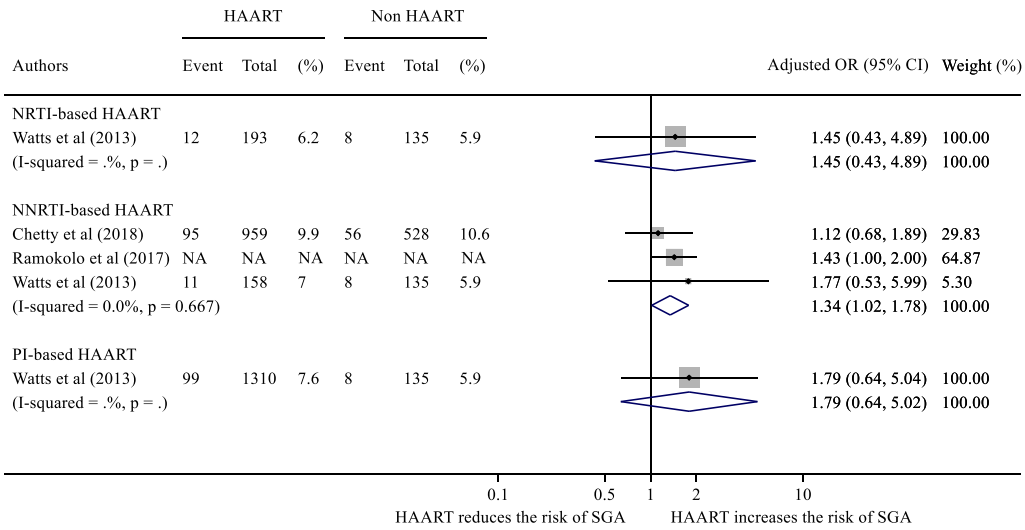


Figure 3.55. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with NRTI, NNRTI and PI-based HAART versus non HAART using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

3.4.5.3.2 Very small for gestational age (VSGA)

HAART versus monotherapy

A prospective cohort conducted in Tanzania, including 2,800 women, showed that HAART was associated with an increased risk of VSGA compared with monotherapy (OR: 1.76, 95% CI: 1.39, 2.22). The study also reported adjusted effect estimates: HAART initiated post-conception (adjusted OR: 1.54, 95% CI: 1.10, 2.19), but not pre-conception (adjusted OR: 1.39, 95% CI: 0.98, 2.00), was associated with an increased risk of VSGA compared with monotherapy [376].

HAART versus non HAART

The pooled unadjusted effect estimates of two cohorts, including 5,001 women, showed no difference in VSGA risk between HAART and non HAART (pooled OR: 1.36, 95% CI: 0.67, 2.76) (Figure 3.56).

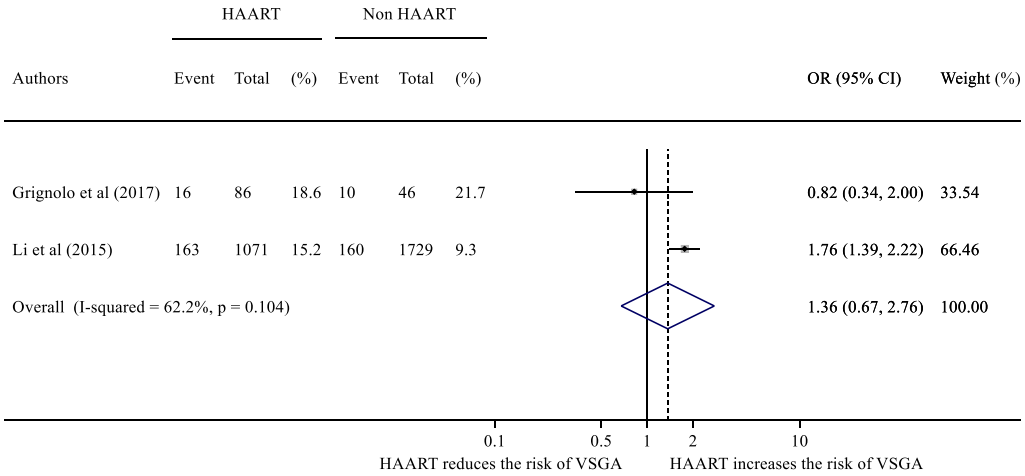


Figure 3.56. Forest plot of risk of very small for gestational age in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

3.4.5.4 Effect of ART complexity on fetal and neonatal mortality

3.4.5.4.1 Stillbirth

HAART versus monotherapy

A retrospective cohort conducted in Botswana, including 7,312 women, showed that HAART was associated with an increased risk of stillbirth compared with monotherapy (OR: 1.84, 95% CI: 1.41, 2.41) [403].

HAART versus non HAART

The meta-analysis of unadjusted effect estimates of two cohorts, including 11,757 women, showed a higher risk of stillbirth in women on HAART than those on non HAART (pooled OR: 1.88, 95% CI: 1.45, 2.42) (Figure 3.57). Of these two cohorts, one reported an adjusted effect estimate suggesting no association between HAART and stillbirth (adjusted OR: 2.27, 95% CI: 0.96, 5.39) [381].

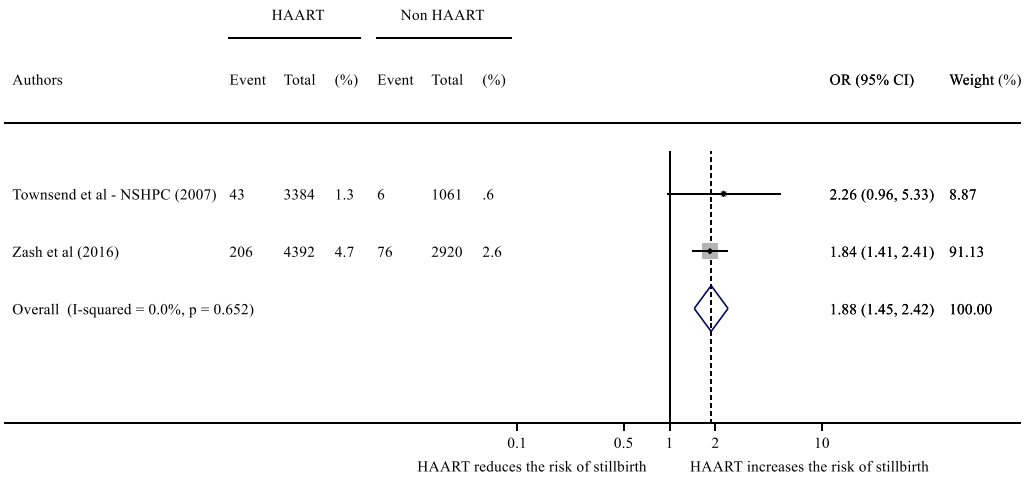


Figure 3.57. Forest plot of risk of stillbirth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio.

3.4.5.4.2 Neonatal death (NND)

HAART versus non HAART

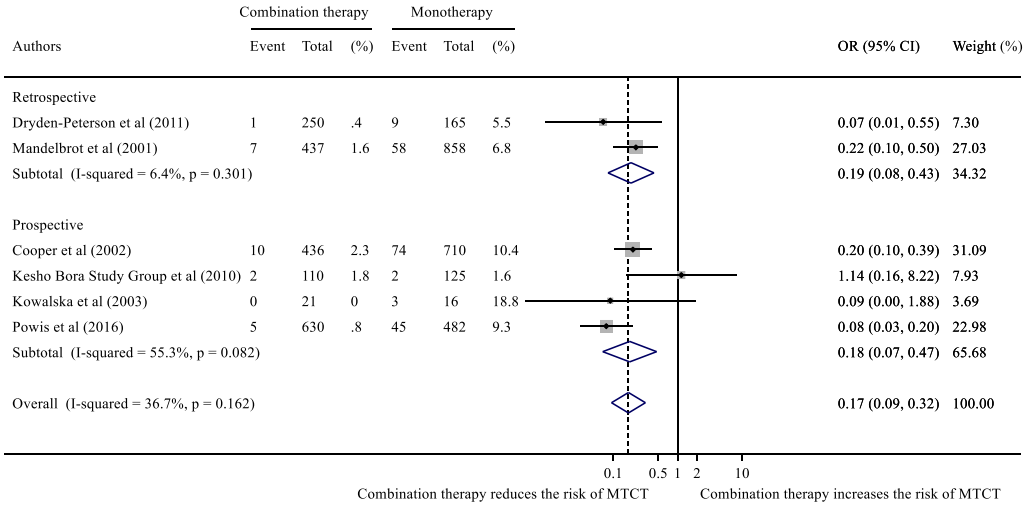
A prospective cohort conducted in the UK and Ireland, including 4,396 women, showed no difference in NND risk between HAART and non HAART (OR: 2.22, 95% CI: 0.50, 9.76) [381].

3.4.5.5 Effect of ART complexity on mother-to-child transmission (MTCT)

Combination therapy versus monotherapy

Six cohorts (two retrospective and four prospective), including 4,240 women, reported the risk of MTCT in HIV-positive pregnant women receiving combination therapy versus those receiving monotherapy; three of the cohorts were conducted in LMICs and three in high-income countries (Figure 3.58). The synthesis of unadjusted effect estimates revealed that combination therapy was associated with a lower risk of MTCT than monotherapy (pooled OR: 0.17, 95% CI: 0.09, 0.32); low heterogeneity (I^2 = 36.7%) was evident (Figure 3.58). The association persisted across cohort design and country-income status: retrospective (pooled OR: 0.19, 95% CI: 0.08, 0.43) and prospective (pooled OR: 0.18, 95% CI: 0.07, 0.47) (Figure 3.58A); LMIC (pooled OR: 0.16, 95% CI: 0.03, 0.85) and high-income country (pooled OR: 0.21, 95% CI: 0.12, 0.34) (Figure 3.58B).

A



B

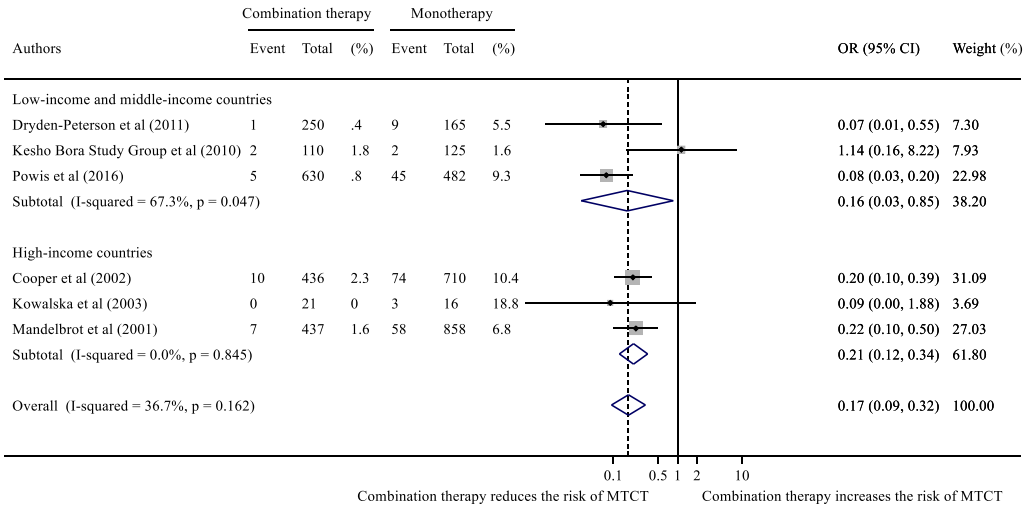


Figure 3.58. Forest plots of risk of mother-to-child transmission in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

Dual therapy versus monotherapy

The pooled unadjusted effect estimates of two cohorts, including 2,191 women, showed a lower risk of MTCT in women on dual therapy compared with those on monotherapy (pooled OR: 0.27, 95% CI: 0.16, 0.48) (Figure 3.59). Of these two cohorts, one reported an adjusted effect estimate showing an association between dual therapy and a lower risk of MTCT (adjusted OR: 0.22, 95% CI: 0.10, 0.49) [414].

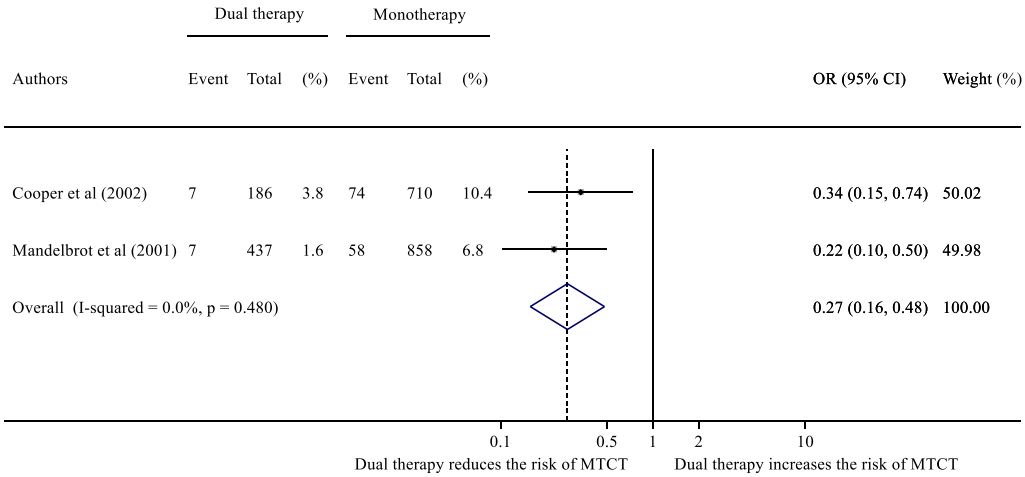


Figure 3.59. Forest plot of risk of mother-to-child transmission in HIV-positive pregnant women treated with dual therapy versus monotherapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

HAART versus monotherapy

The meta-analysis of unadjusted effect estimates of five cohorts (one retrospective and four prospective), including 2,759 women, showed that HAART was associated with a lower risk of MTCT than monotherapy (pooled OR: 0.12, 95% CI: 0.05, 0.30), with low heterogeneity (I^2 = 34.9%) (Figure 3.60). The association remained irrespective of country-income status: LMIC (pooled OR: 0.16, 95% CI: 0.03, 0.85) and high-income country (pooled OR: 0.10, 95% CI: 0.03, 0.30) (Figure 3.60).

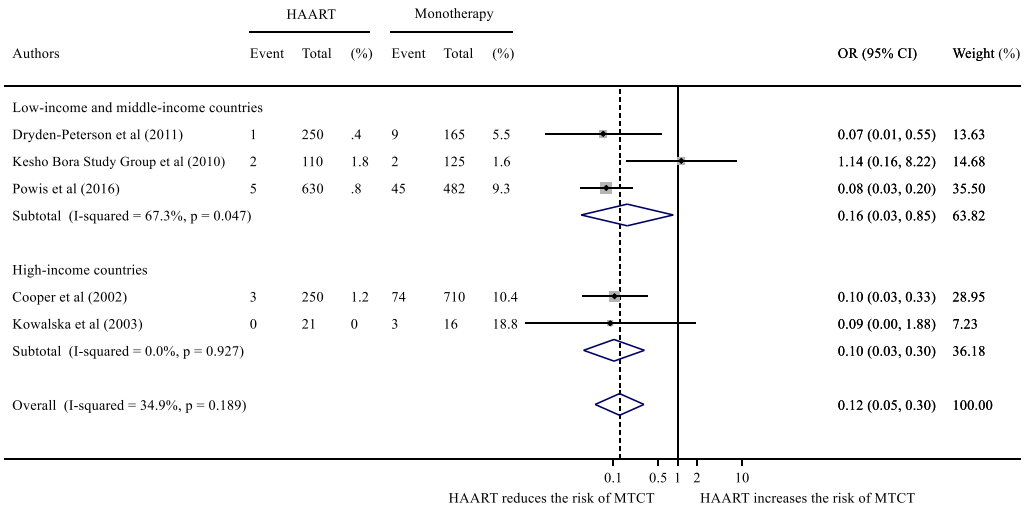


Figure 3.60. Forest plot of risk of mother-to-child transmission in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data, by country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

HAART versus dual therapy

A prospective cohort conducted in the USA, including 436 women, showed no difference in MTCT risk between HAART and dual therapy (OR: 0.31, 95% CI: 0.08, 1.22) [420].

HAART versus non HAART

The risk of MTCT in HIV-positive pregnant women receiving HAART versus those receiving non HAART was reported in six cohorts (two retrospective and four prospective), including 3,431 women; three of the cohorts were conducted in LMICs and three in high-income countries (Figure 3.61). The pooled unadjusted effect estimates showed that HAART was associated with a lower risk of MTCT than non HAART (pooled OR: 0.11, 95% CI: 0.05, 0.27), with low heterogeneity (I^2 = 35.4%) (Figure 3.61). The association persisted across cohort design and

country-income status: retrospective (pooled OR: 0.04, 95% CI: 0.01, 0.23) and prospective (pooled OR: 0.15, 95% CI: 0.05, 0.44) (Figure 3.61A); LMIC (pooled OR: 0.16, 95% CI: 0.03, 0.85) and high-income country (pooled OR: 0.09, 95% CI: 0.03, 0.26) (Figure 3.61B).

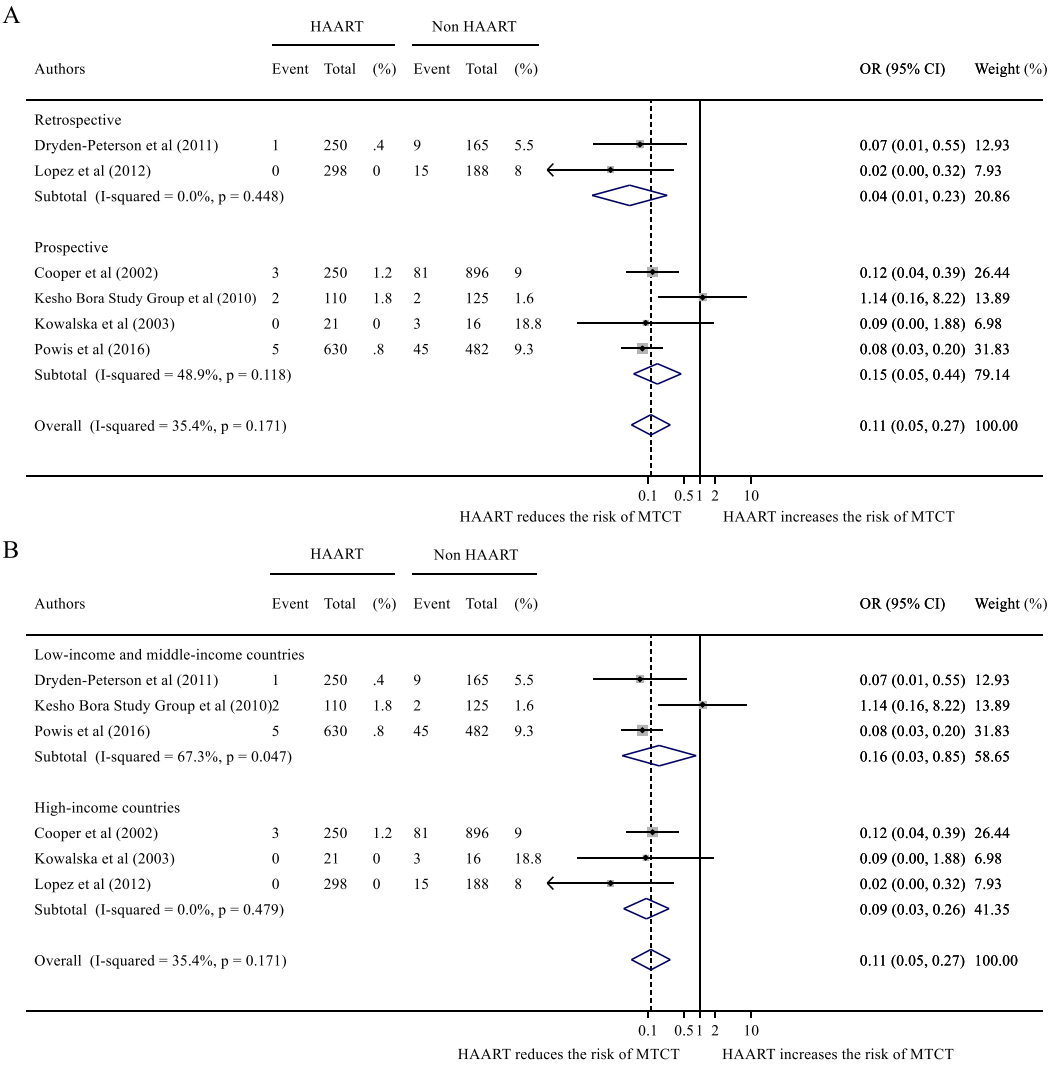


Figure 3.61. Forest plots of risk of mother-to-child transmission in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

3.4.5.6 Summary of meta-analysis results

The summary of meta-analysis results for the effect of ART complexity on perinatal outcomes is provided in Appendix 3.9: Tables 3.6 and 3.7.

3.4.6 Effect of ART class on perinatal outcomes

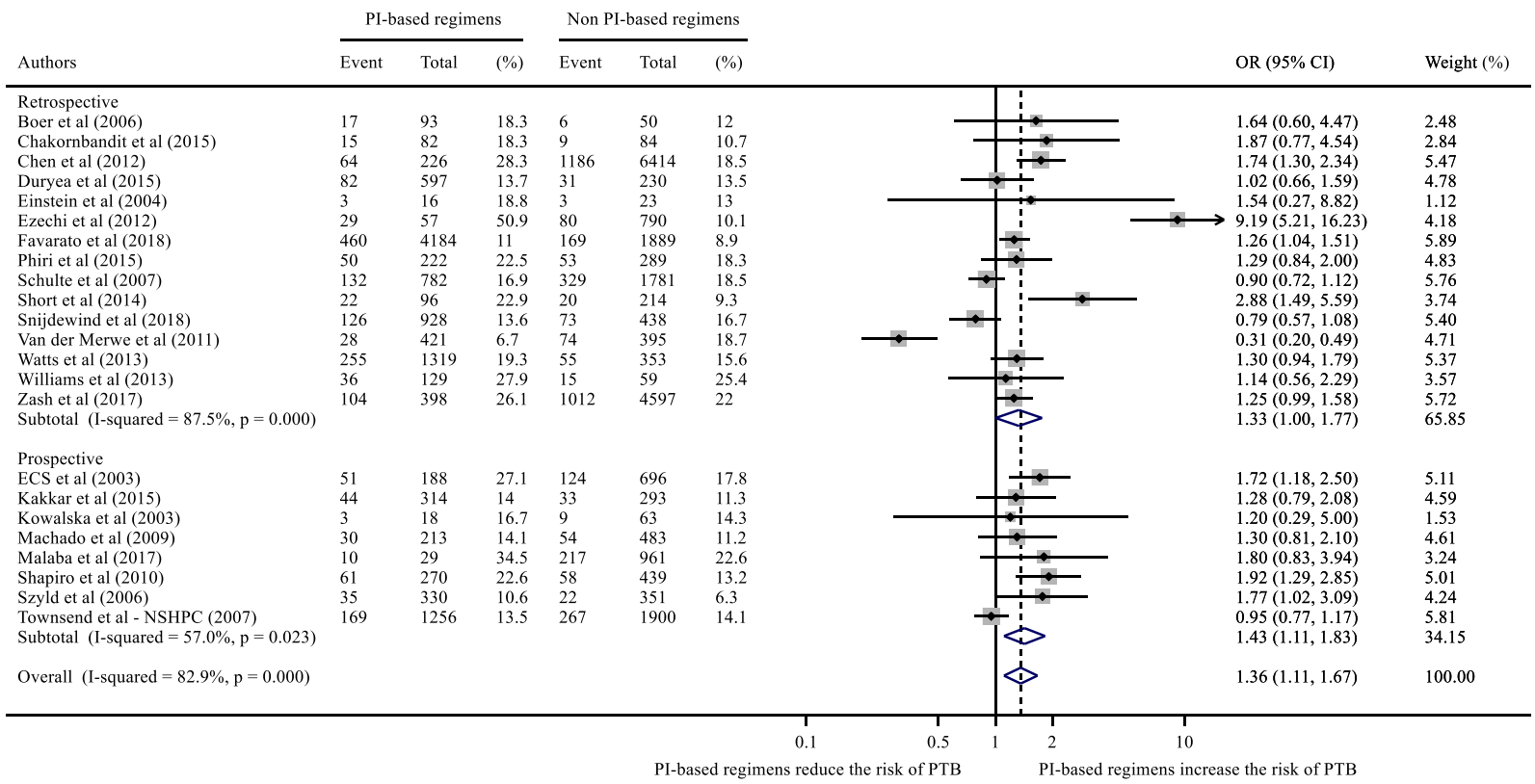
The fourth aim was investigated by conducting pairwise meta-analyses assessing the risk of adverse perinatal outcomes in HIV-positive pregnant women treated with different ART classes. The exposure group was HIV-positive pregnant women treated with PI, and comparator group was those treated with non PI-based (NRTI, NNRTI and INSTI) regimens.

3.4.6.1 Effect of ART class on gestational age at delivery

3.4.6.1.1 Preterm birth (PTB)

The risk of PTB in HIV-positive pregnant women on PI versus those on non PI-based regimens was reported by 23 cohorts (15 retrospective and eight prospective) including 34,960 women; nine cohorts were conducted in LMICs and 14 in high-income countries (Figure 3.62). The pooled unadjusted effect estimates showed an increased risk of PTB in women on PI compared with those on non PI-based regimens (pooled OR: 1.36, 95% CI: 1.11, 1.67), a high degree of heterogeneity (I^2 = 82.9%) was evident (Figure 3.62). The finding persisted in the sub-group analyses of prospective (pooled OR: 1.43, 95% CI: 1.11, 1.83) and retrospective cohorts (pooled OR: 1.33, 95% CI: 1.00, 1.77) at borderline statistical significance; a high degree of heterogeneity (I^2 = 87.5%) was evident in retrospective cohorts only (Figure 3.62A). PI-based regimens remained associated with a higher risk of PTB at borderline statistical significance in LMIC (pooled OR: 1.63, 95% CI: 0.99, 2.66) and high-income country (pooled OR: 1.17, 95% CI: 1.00, 1.37); a high degree of heterogeneity (I^2 = 91.2%) was evident in LMIC only (Figure 3.62B).

A


PI-based regimens
Non PI-based regimens
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Boer et al (2006) 17 93 18.3 6 50 12 1.64 (0.60, 4.47) 2.48
Chakornbandit et al (2015) 15 82 18.3 9 84 10.7 1.87 (0.77, 4.54) 2.84
Chen et al (2012) 64 226 28.3 1186 6414 18.5 1.74 (1.30, 2.34) 5.47
Duryea et al (2015) 82 597 13.7 31 230 13.5 1.02 (0.66, 1.59) 4.78
Einstein et al (2004) 3 16 18.8 3 23 13 1.54 (0.27, 8.82) 1.12
Ezechi et al (2012) 29 57 50.9 80 790 10.1 9.19 (5.21, 16.23) 4.18
Favarato et al (2018) 460 4184 11 169 1889 8.9 1.26 (1.04, 1.51) 5.89
Phiri et al (2015) 50 222 22.5 53 289 18.3 1.29 (0.84, 2.00) 4.83
Schulte et al (2007) 132 782 16.9 329 1781 18.5 0.90 (0.72, 1.12) 5.76
Short et al (2014) 22 96 22.9 20 214 9.3 2.88 (1.49, 5.59) 3.74
Snijdewind et al (2018) 126 928 13.6 73 438 16.7 0.79 (0.57, 1.08) 5.40
Van der Merwe et al (2011) 28 421 6.7 74 395 18.7 0.31 (0.20, 0.49) 4.71
Watts et al (2013) 255 1319 19.3 55 353 15.6 1.30 (0.94, 1.79) 5.37
Williams et al (2013) 36 129 27.9 15 59 25.4 1.14 (0.56, 2.29) 3.57
Zash et al (2017) 104 398 26.1 1012 4597 22 1.25 (0.99, 1.58) 5.72
Subtotal (I-squared = 87.5%, p = 0.000) 1.33 (1.00, 1.77) 65.85
Prospective
ECS et al (2003) 51 188 27.1 124 696 17.8 1.72 (1.18, 2.50) 5.11
Kakkar et al (2015) 44 314 14 33 293 11.3 1.28 (0.79, 2.08) 4.59
Kowalska et al (2003) 3 18 16.7 9 63 14.3 1.20 (0.29, 5.00) 1.53
Machado et al (2009) 30 213 14.1 54 483 11.2 1.30 (0.81, 2.10) 4.61
Malaba et al (2017) 10 29 34.5 217 961 22.6 1.80 (0.83, 3.94) 3.24
Shapiro et al (2010) 61 270 22.6 58 439 13.2 1.92 (1.29, 2.85) 5.01
Szyld et al (2006) 35 330 10.6 22 351 6.3 1.77 (1.02, 3.09) 4.24
Townsend et al - NSHPC (2007) 169 1256 13.5 267 1900 14.1 0.95 (0.77, 1.17) 5.81
Subtotal (I-squared = 57.0%, p = 0.023) 1.43 (1.11, 1.83) 34.15
Overall (I-squared = 82.9%, p = 0.000) 1.36 (1.11, 1.67) 100.00
0.1
0.5
1
2
10
PI-based regimens reduce the risk of PTB
PI-based regimens increase the risk of PTB

B

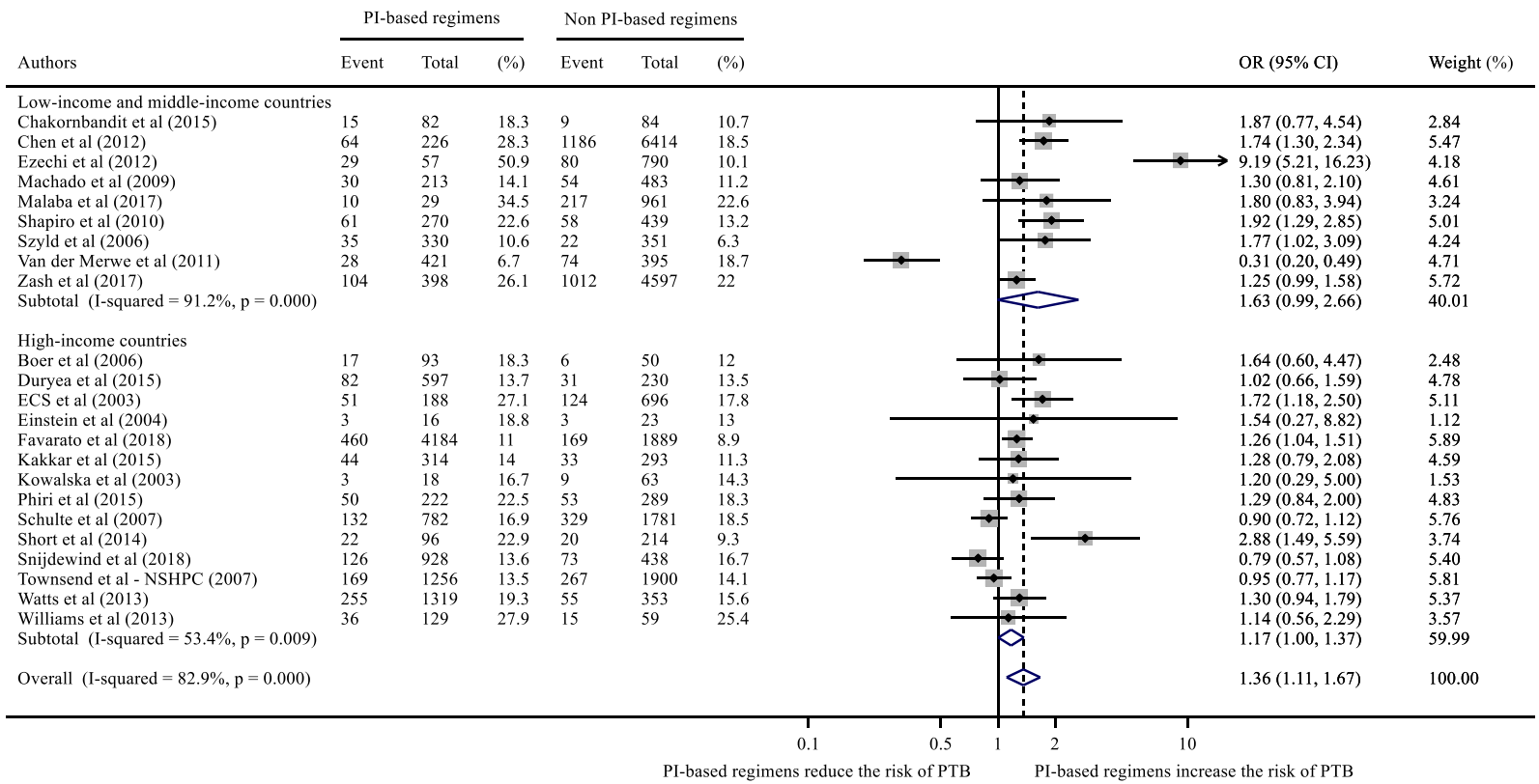


Figure 3.62. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

The contour-enhanced funnel plot in Figure 3.63 seems asymmetric, and shows that the hypothetical missing studies appear to fall in the regions of both statistical significance and non-significance. These findings suggest that publication bias is not the only reason for the observed asymmetric funnel plot. The Harbord's test had a *P* value of 0.086, indicating evidence of small-study effects (at borderline statistical significance).

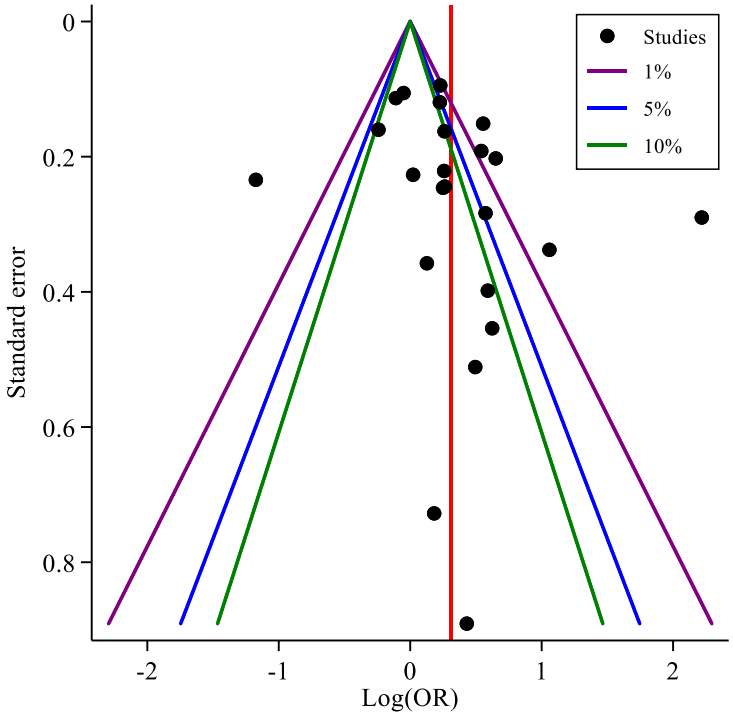


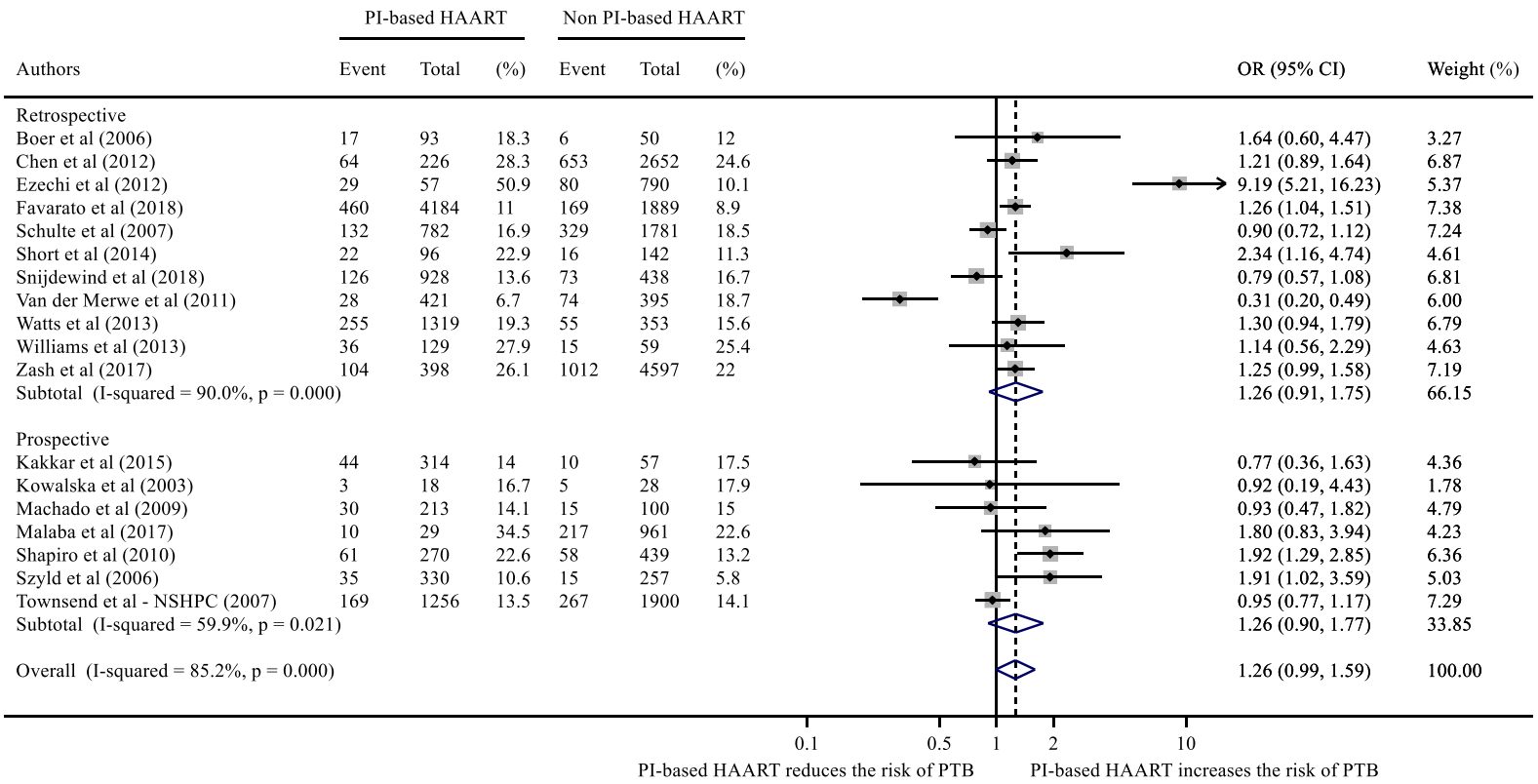
Figure 3.63. Contour-enhanced funnel plot of the 23 cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data. Solid black circles correspond to the 23 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The contour-enhanced funnel plot of prospective, but not retrospective cohorts, seems asymmetric (Appendix 3.10: Figure 3.49); the Harbord's tests had *P* values of 0.097 and 0.256 for prospective and retrospective cohorts, respectively. The contour-enhanced funnel plots of LMIC and high-income country seem

symmetric (Appendix 3.10: Figure 3.50); the Harbord's tests did not show any evidence of small-study effects in both LMIC (P = 0.306) and high-income country (P = 0.177). However, these findings should be interpreted cautiously because there were few studies in the prospective (n=8) and LMIC (n=9) sub-groups.

Of the 23 cohorts, 18 (11 retrospective and seven prospective) specified HAART as an ART regimen administered to the women; of these 18 cohorts, eight were conducted in LMICs and 10 in high-income countries (Figure 3.64). Among women on HAART, PI was associated with an increased risk of PTB at borderline statistical significance (pooled OR: 1.26, 95% CI: 0.99, 1.59) compared with non PI; a high degree of heterogeneity (I^2 = 85.2%) was evident (Figure 3.64). However, in sub-group analyses by cohort design and country-income status, PI-based HAART was not associated with PTB: retrospective (pooled OR: 1.26, 95% CI: 0.91, 1.75) and prospective (pooled OR: 1.26, 95% CI: 0.90, 1.77) (Figure 3.64A); LMIC (pooled OR: 1.49, 95% CI: 0.86, 2.58) and high-income country (pooled OR: 1.07, 95% CI: 0.90, 1.26) (Figure 3.64B). A high degree of heterogeneity was observed in retrospective cohorts (I^2 = 90%) (Figure 3.64A) and LMIC (I^2 = 92.3%) (Figure 3.64B).

A


PI-based HAART
Non PI-based HAART
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Boer et al (2006) 17 93 18.3 6 50 12 1.64 (0.60, 4.47) 3.27
Chen et al (2012) 64 226 28.3 653 2652 24.6 1.21 (0.89, 1.64) 6.87
Ezechi et al (2012) 29 57 50.9 80 790 10.1 9.19 (5.21, 16.23) 5.37
Favarato et al (2018) 460 4184 11 169 1889 8.9 1.26 (1.04, 1.51) 7.38
Schulte et al (2007) 132 782 16.9 329 1781 18.5 0.90 (0.72, 1.12) 7.24
Short et al (2014) 22 96 22.9 16 142 11.3 2.34 (1.16, 4.74) 4.61
Snijdewind et al (2018) 126 928 13.6 73 438 16.7 0.79 (0.57, 1.08) 6.81
Van der Merwe et al (2011) 28 421 6.7 74 395 18.7 0.31 (0.20, 0.49) 6.00
Watts et al (2013) 255 1319 19.3 55 353 15.6 1.30 (0.94, 1.79) 6.79
Williams et al (2013) 36 129 27.9 15 59 25.4 1.14 (0.56, 2.29) 4.63
Zash et al (2017) 104 398 26.1 1012 4597 22 1.25 (0.99, 1.58) 7.19
Subtotal (I-squared = 90.0%, p = 0.000) 1.26 (0.91, 1.75) 66.15
Prospective
Kakkar et al (2015) 44 314 14 10 57 17.5 0.77 (0.36, 1.63) 4.36
Kowalska et al (2003) 3 18 16.7 5 28 17.9 0.92 (0.19, 4.43) 1.78
Machado et al (2009) 30 213 14.1 15 100 15 0.93 (0.47, 1.82) 4.79
Malaba et al (2017) 10 29 34.5 217 961 22.6 1.80 (0.83, 3.94) 4.23
Shapiro et al (2010) 61 270 22.6 58 439 13.2 1.92 (1.29, 2.85) 6.36
Szyld et al (2006) 35 330 10.6 15 257 5.8 1.91 (1.02, 3.59) 5.03
Townsend et al - NSHPC (2007) 169 1256 13.5 267 1900 14.1 0.95 (0.77, 1.17) 7.29
Subtotal (I-squared = 59.9%, p = 0.021) 1.26 (0.90, 1.77) 33.85
Overall (I-squared = 85.2%, p = 0.000) 1.26 (0.99, 1.59) 100.00
0.1
0.5
1
2
10
PI-based HAART reduces the risk of PTB
PI-based HAART increases the risk of PTB

B

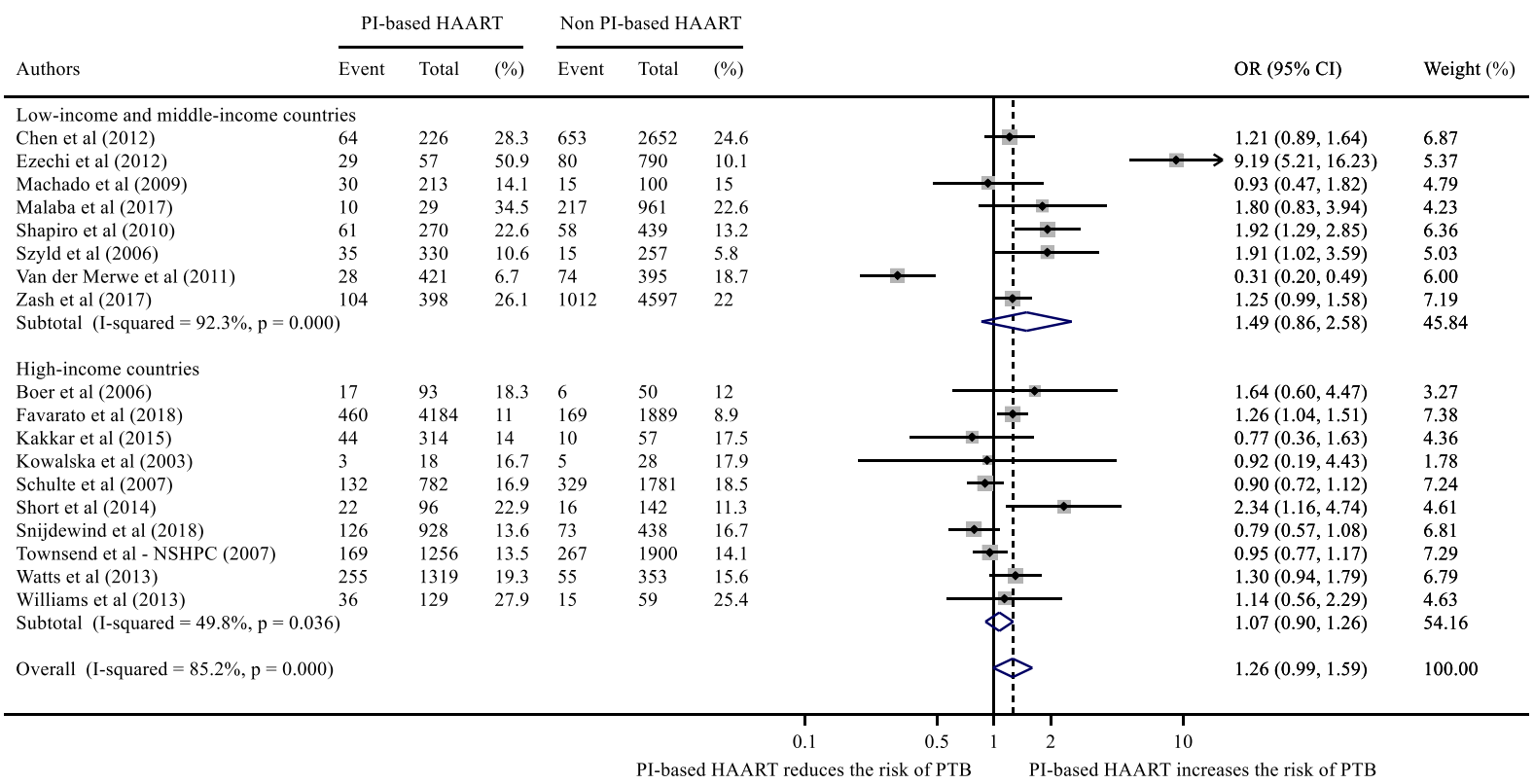
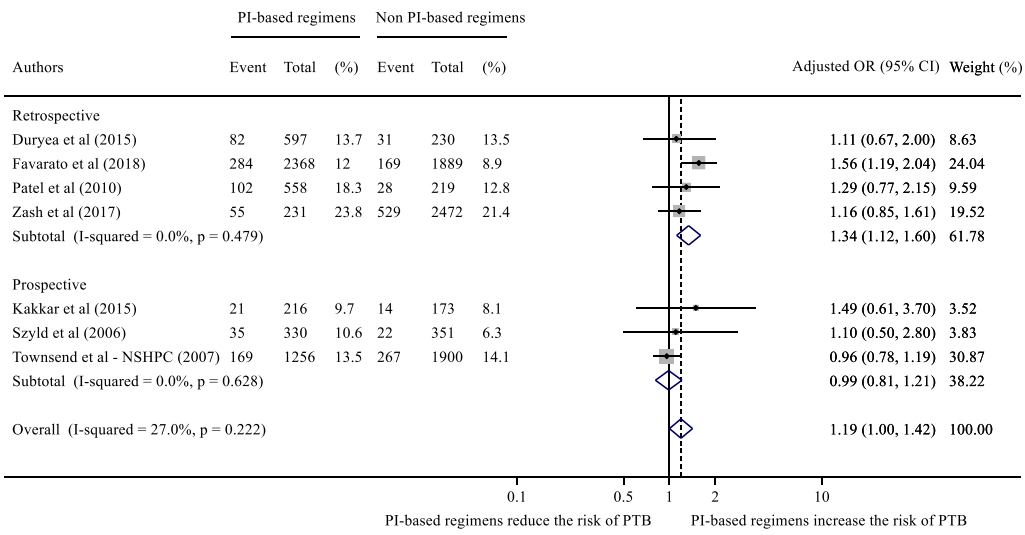


Figure 3.64. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

The pooled adjusted effect estimates including seven cohorts (four retrospective and three prospective) showed an association between PI-based regimens and an increased risk of PTB at borderline statistical significance (pooled adjusted OR: 1.19, 95% CI: 1.00, 1.42), with low heterogeneity (I^2 = 27%) (Figure 3.65). Sub-group analysis by cohort design showed an association between PI-based regimens and an increased risk of PTB in retrospective (pooled adjusted OR: 1.34, 95% CI: 1.12, 1.60), but not prospective cohorts (pooled adjusted OR: 0.99, 95% CI: 0.81, 1.21) (Figure 3.65A). Sub-group analysis by country-income status showed no association between PI-based regimens and PTB in either LMIC (pooled adjusted OR: 1.15, 95% CI: 0.85, 1.55) or high-income country (pooled adjusted OR: 1.22, 95% CI: 0.95, 1.57) (Figure 3.65B).

A



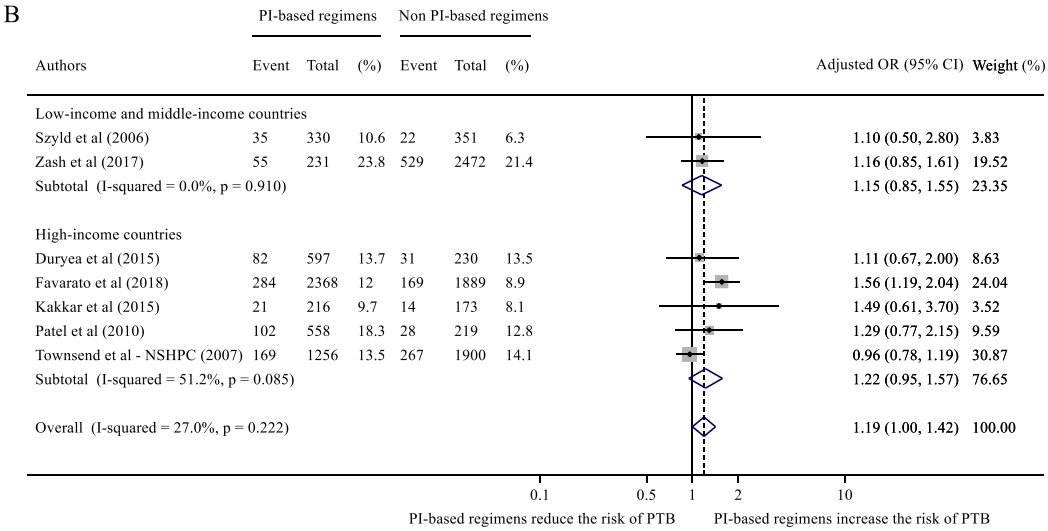


Figure 3.65. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using adjusted effect estimates, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

Of the seven cohorts with adjusted effect estimates, four (two retrospective and two prospective) used HAART, and the meta-analysis showed no association between PI-based HAART and PTB (pooled adjusted OR: 1.21, 95% CI: 0.93, 1.59), with moderate heterogeneity (I^2 = 62.6%) (Figure 3.66). Sub-group analysis by cohort design showed an association between PI-based HAART and an increased risk of PTB in retrospective (pooled adjusted OR: 1.36, 95% CI: 1.02, 1.82), but not prospective cohorts (pooled adjusted OR: 0.98, 95% CI: 0.80, 1.21) (Figure 3.66). Sub-group analysis by country-income status was not performed because only one cohort was conducted in an LMIC [96].

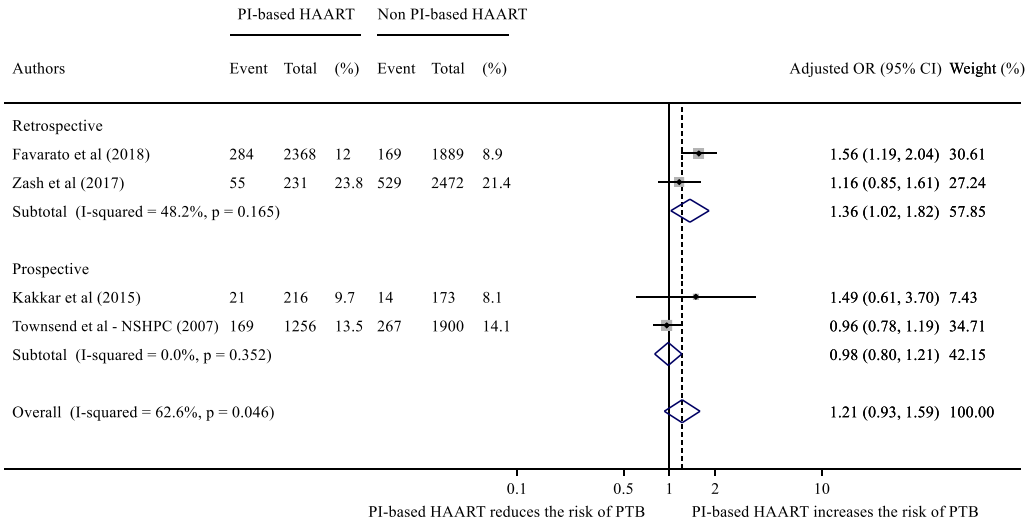


Figure 3.66. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based HAART using adjusted effect estimates, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

3.4.6.1.2 Spontaneous preterm birth (sPTB)

Three retrospective cohorts including 3,296 women reported the risk of sPTB in women receiving PI versus non PI-based regimens; however, one cohort [380] including 777 women was excluded due to the possibility of overlap with another cohort [372]. The remaining two cohorts used HAART, and the pooled unadjusted effect estimates showed no association between PI-based HAART and sPTB (pooled OR: 3.35, 95% CI: 0.46, 24.38) (Figure 3.67). The excluded cohort was the only one reporting an adjusted effect estimate, and showed no association between PI-based regimens and sPTB (adjusted OR: 1.22, 95% CI: 0.70, 2.12) [380].

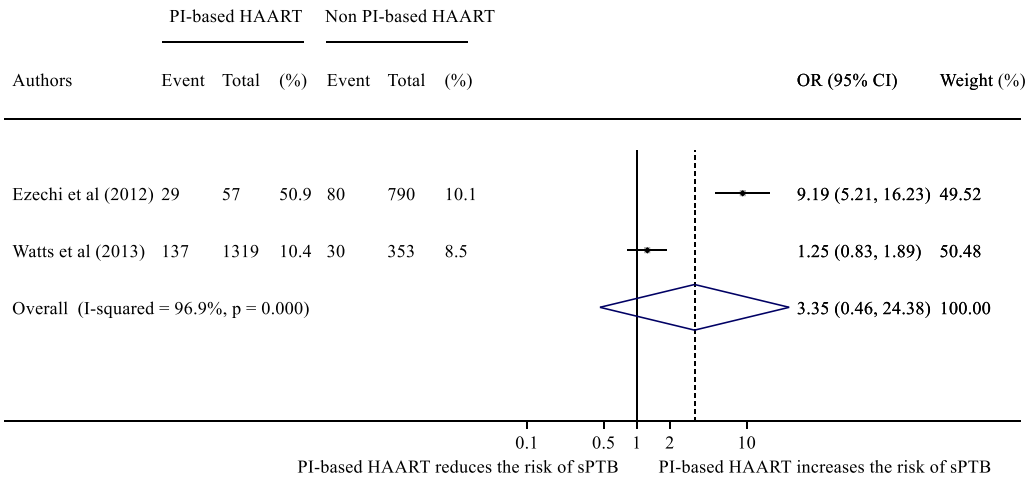


Figure 3.67. Forest plot of risk of spontaneous preterm birth in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; sPTB, spontaneous preterm birth.

3.4.6.1.3 Very preterm birth (VPTB)

The pooled unadjusted effect estimates of six cohorts (four retrospective and two prospective), including 9,348 women, showed no difference in VPTB risk between PI and non PI-based regimens (pooled OR: 1.37, 95% CI: 0.90, 2.11), with low heterogeneity (I^2 = 25.3%) (Figure 3.68). The finding persisted across cohort design: retrospective (pooled OR: 1.33, 95% CI: 0.77, 2.31) and prospective (pooled OR: 1.90, 95% CI: 0.70, 5.17) (Figure 3.68A). However, the sub-group analysis of cohorts conducted in LMICs (pooled OR: 1.51, 95% CI: 1.03, 2.21), but not in high-income countries (pooled OR: 1.44, 95% CI: 0.52, 3.98), showed an association between PI-based regimens and an increased risk of VPTB (Figure 3.68B).

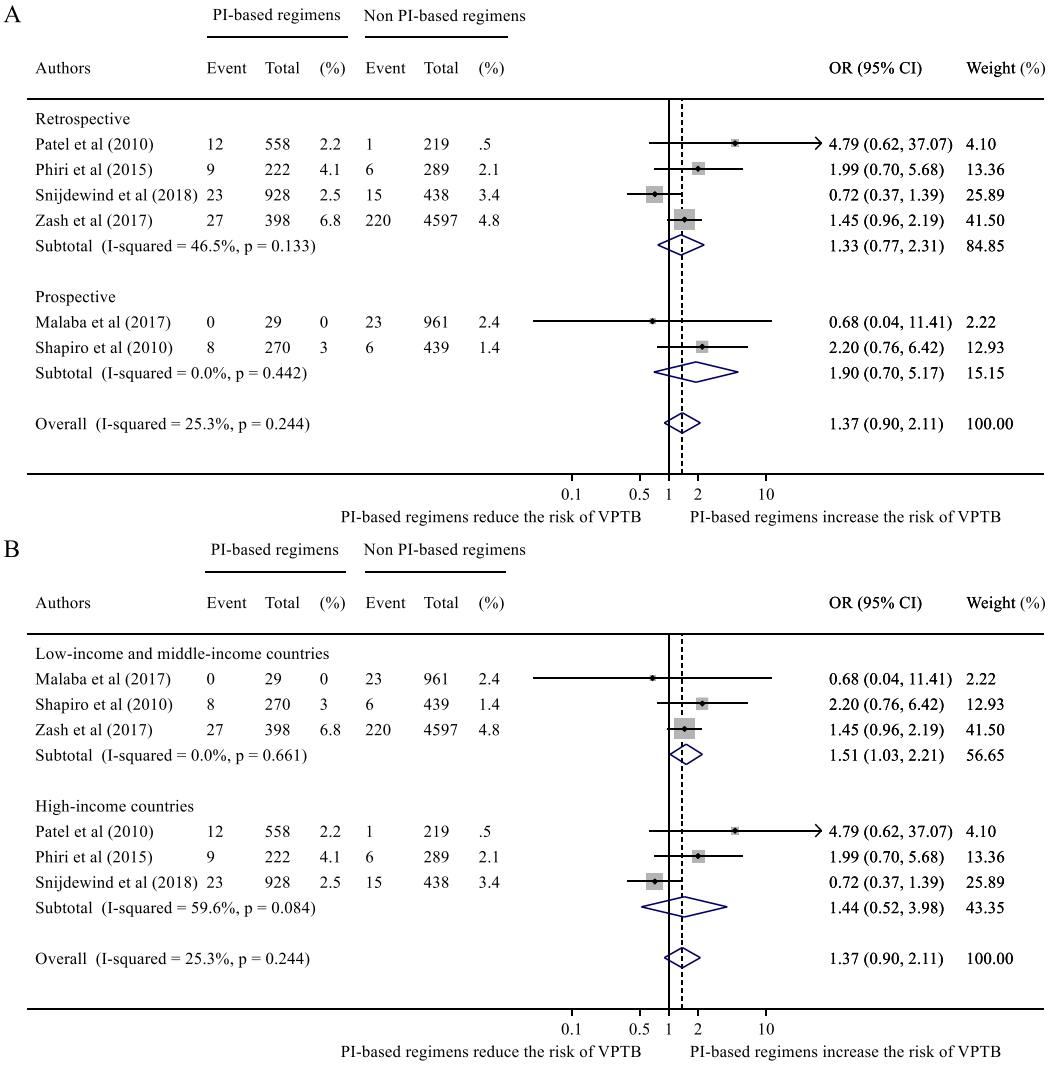


Figure 3.68. Forest plots of risk of very preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VPTB, very preterm birth.

Of the six cohorts, four (two retrospective and two prospective) used HAART, and the meta-analysis showed similar findings to the above results: 1) overall, PI-based HAART was not associated with VPTB (pooled OR: 1.21, 95% CI: 0.75, 1.98) (Figure 3.69); 2) this finding was consistently observed across cohort design: retrospective (pooled OR: 1.07, 95% CI: 0.54, 2.12) and prospective

(pooled OR: 1.90, 95% CI: 0.70, 5.17) (Figure 3.69). Sub-group analysis by country-income status was not performed because only one cohort was conducted in a high-income country [417].

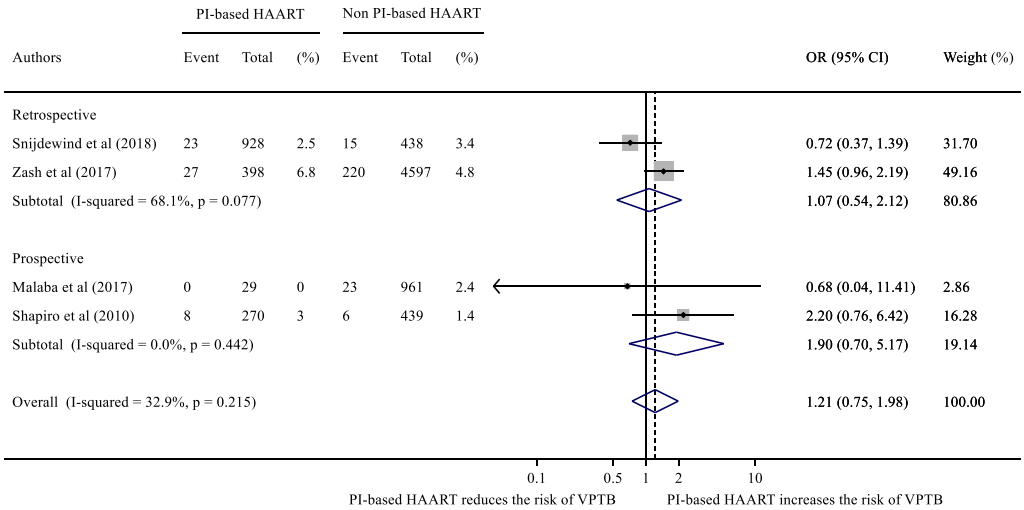


Figure 3.69. Forest plot of risk of very preterm birth in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VPTB, very preterm birth.

A retrospective cohort, conducted in Botswana, reported an adjusted effect estimate suggesting no difference in VPTB risk between PI and non PI-based HAART (adjusted OR: 1.38, 95% CI: 0.75, 2.61) [96].

3.4.6.2 Effect of ART class on birth weight

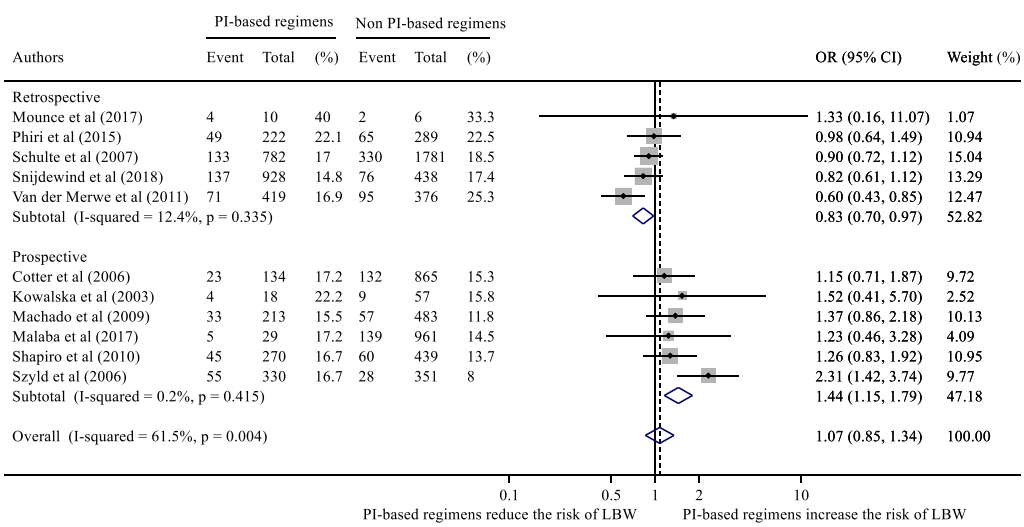
3.4.6.2.1 Low birth weight (LBW)

The risk of LBW in HIV-positive pregnant women on PI versus those on non PI-based regimens was reported in 11 cohorts (five retrospective and six prospective), including 9,401 women; five cohorts were conducted in LMICs and six in high-income countries (Figure 3.70). The meta-analysis of unadjusted effect

estimates showed no difference in LBW risk between PI and non PI-based regimens (pooled OR: 1.07, 95% CI: 0.85, 1.34), with moderate heterogeneity (I^2 = 61.5%) (Figure 3.70). In retrospective cohorts, PI-based regimens were associated with a decreased risk of LBW (pooled OR: 0.83, 95% CI: 0.70, 0.97); however, in prospective cohorts, PI-based regimens were associated with an increased risk of LBW (pooled OR: 1.44, 95% CI: 1.15, 1.79) (Figure 3.70A). In sub-group analysis by country-income status, both LMIC (pooled OR: 1.23, 95% CI: 0.74, 2.03) and high-income country (pooled OR: 0.92, 95% CI: 0.79, 1.08) showed no association between PI-based regimens and LBW (Figure 3.70B).

The contour-enhanced funnel plot in Figure 3.71 is rather symmetric, indicating no evidence of publication bias; the Harbord's test had a *P* value of 0.202, indicating no evidence of small-study effects.

A



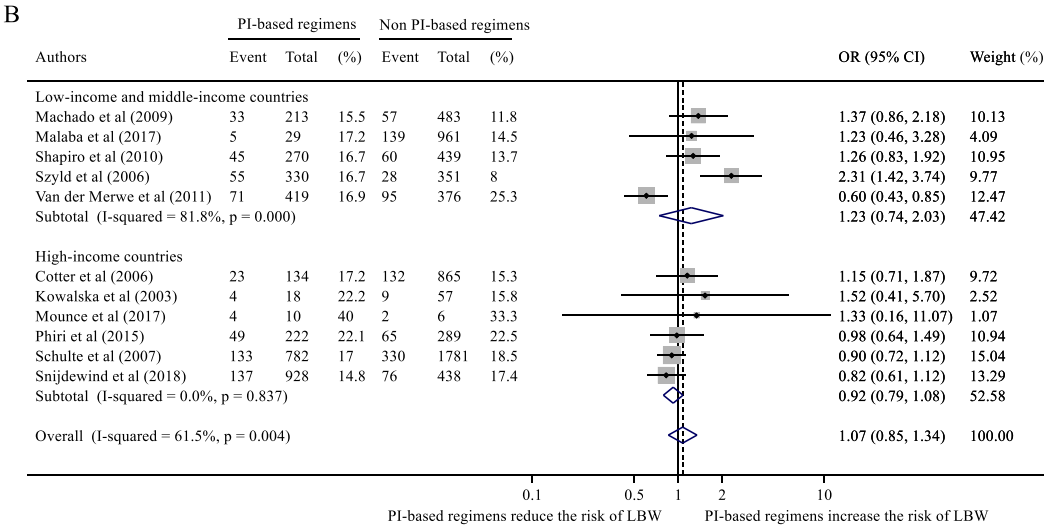


Figure 3.70. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

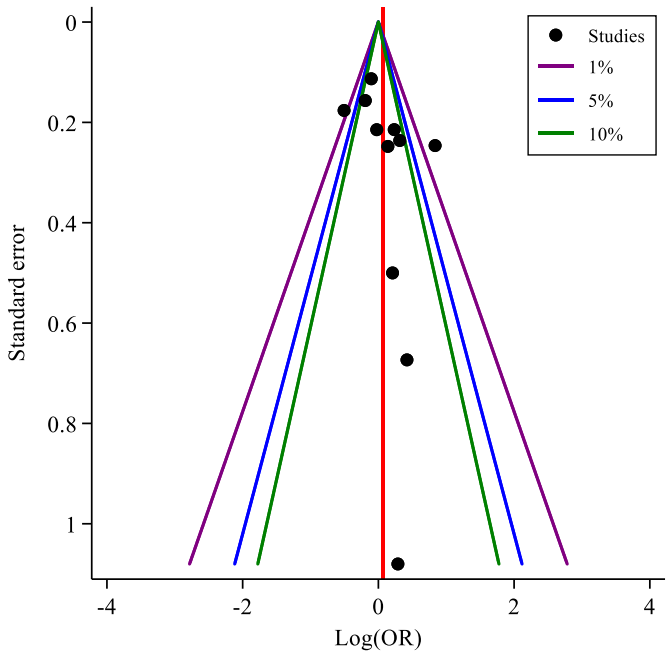
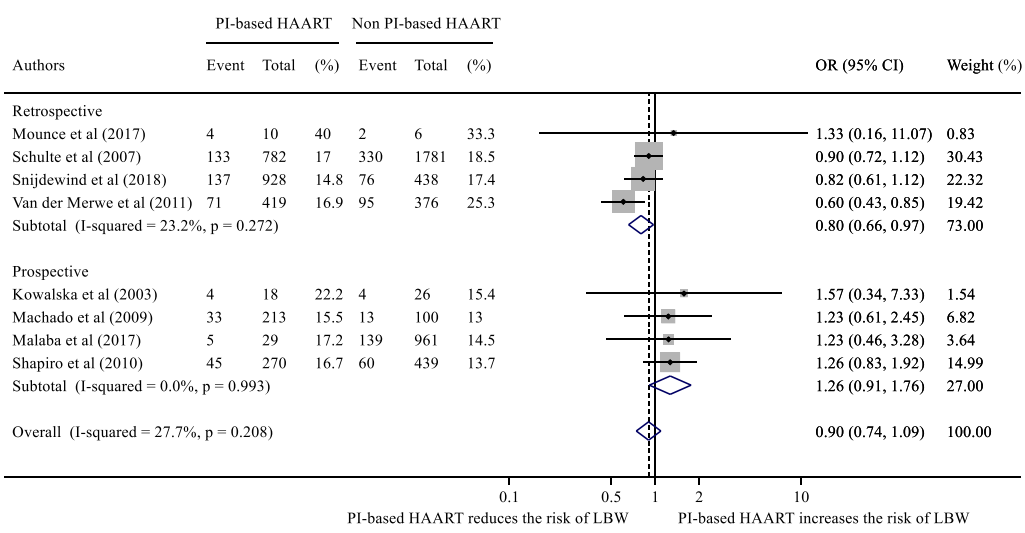


Figure 3.71. Contour-enhanced funnel plot of the 11 cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data. Solid black circles correspond to the 11 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 11 cohorts, eight (four retrospective and four prospective) used HAART, and the synthesis of unadjusted effect estimates showed no association between PI-based HAART and LBW (pooled OR: 0.90, 95% CI: 0.74, 1.09), with low heterogeneity (I^2 = 27.7%) (Figure 3.72). However, in the sub-group analysis of retrospective (pooled OR: 0.80, 95% CI: 0.66, 0.97), but not prospective cohorts (pooled OR: 1.26, 95% CI: 0.91, 1.76), PI-based HAART was associated with a decreased risk of LBW (Figure 3.72A). In sub-group analysis by country-income status, PI-based HAART remained not associated with LBW in both LMIC (pooled OR: 0.98, 95% CI: 0.61, 1.56) and high-income country (pooled OR: 0.88, 95% CI: 0.74, 1.06) (Figure 3.72B).

A



B

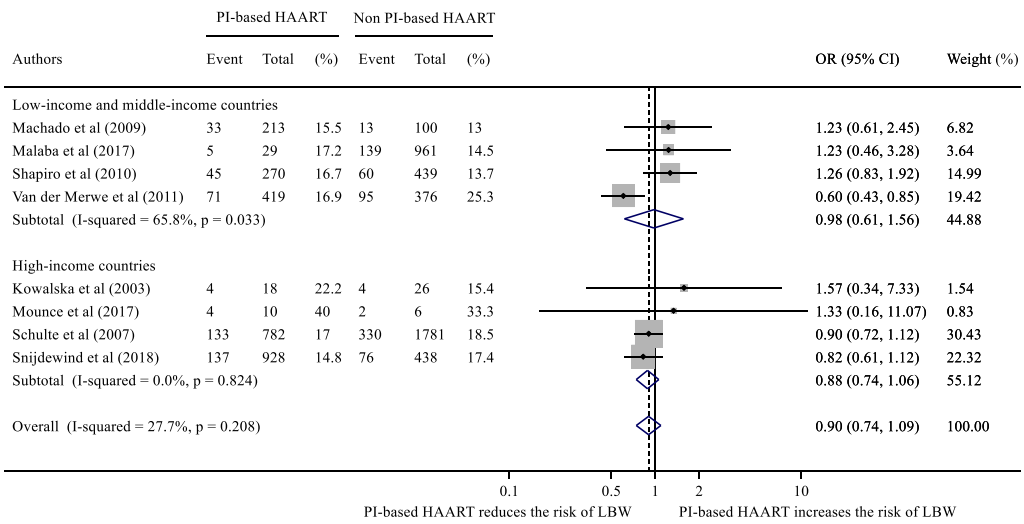


Figure 3.72. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

The meta-analysis adjusted effect estimates including two cohorts conducted in high-income countries showed no difference in LBW risk between PI and non PI-based regimens (pooled adjusted OR: 1.11, 95% CI: 0.67, 1.84) (Figure 3.73).

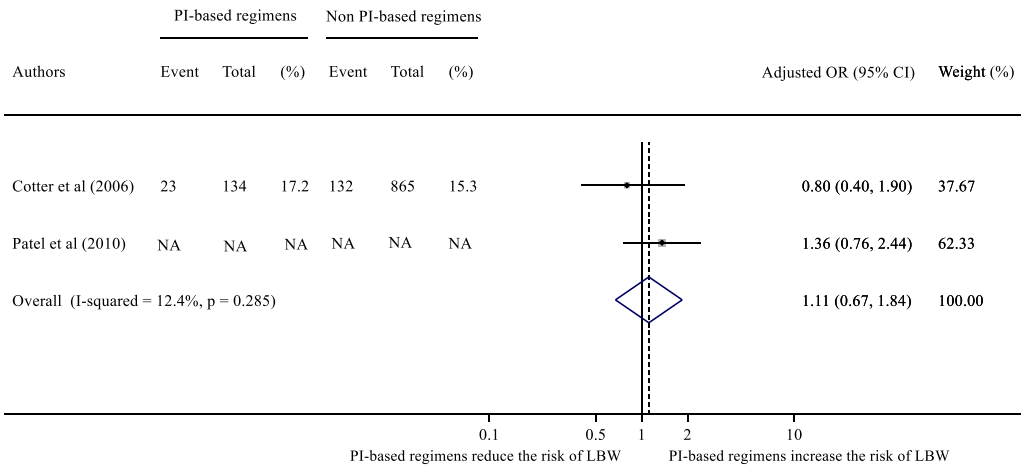


Figure 3.73. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with PI versus non PI-based regimes using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; NA, not available; OR, odds ratio; PI, protease inhibitor.

3.4.6.2.2 Very low birth weight (VLBW)

The meta-analysis of unadjusted effect estimates of six cohorts (three retrospective and three prospective), including 5,370 women, showed no association between PI-based regimens and VLBW (pooled OR: 0.81, 95% CI: 0.43, 1.52), with low heterogeneity (I^2 = 31.5%) (Figure 3.74). The finding persisted across cohort design and country-income status: retrospective (pooled OR: 1.12, 95% CI: 0.38, 3.26) and prospective (pooled OR: 0.55, 95% CI: 0.21, 1.46) (Figure 3.74A); LMIC (pooled OR: 0.88, 95% CI: 0.21, 3.69) and high-income country (pooled OR: 0.76, 95% CI: 0.35, 1.63) (Figure 3.74B).

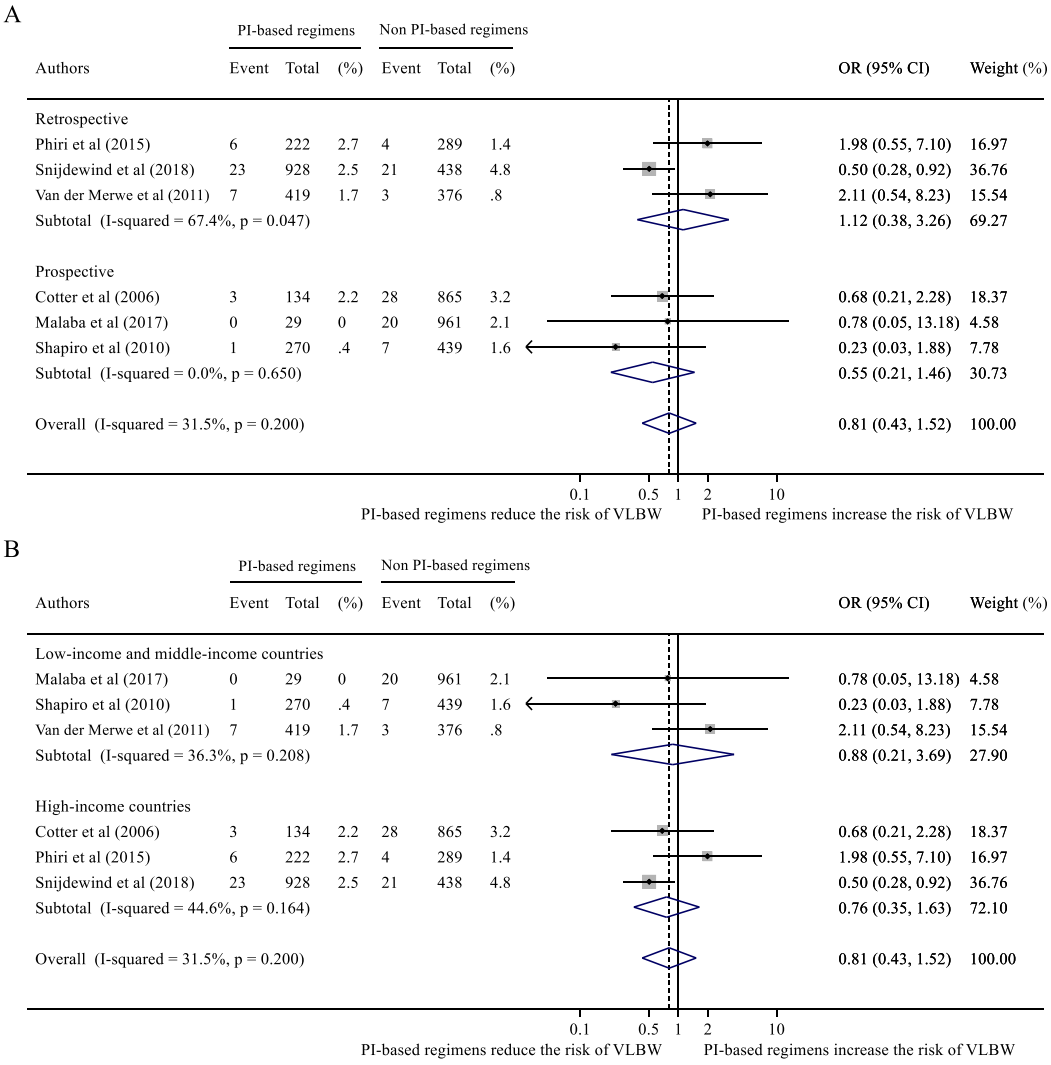


Figure 3.74. Forest plots of risk of very low birth weight in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VLBW, very low birth weight.

Of the six cohorts, four (two retrospective and two prospective) used HAART, and the meta-analyses of unajdusted effect esimates showed similar findings to the above results: 1) overall, PI-based HAART was not associated with VLBW (pooled OR: 0.68, 95% CI: 0.29, 1.58) (Figure 3.75); 2) this finding persisted across cohort design: retrospective (pooled OR: 0.90, 95% CI: 0.23, 3.60) and

prospective (pooled OR: 0.35, 95% CI: 0.07, 1.91) (Figure 3.75). Sub-group analysis by country-income status was not performed because only one of the cohorts was conducted in a high-income country [417].

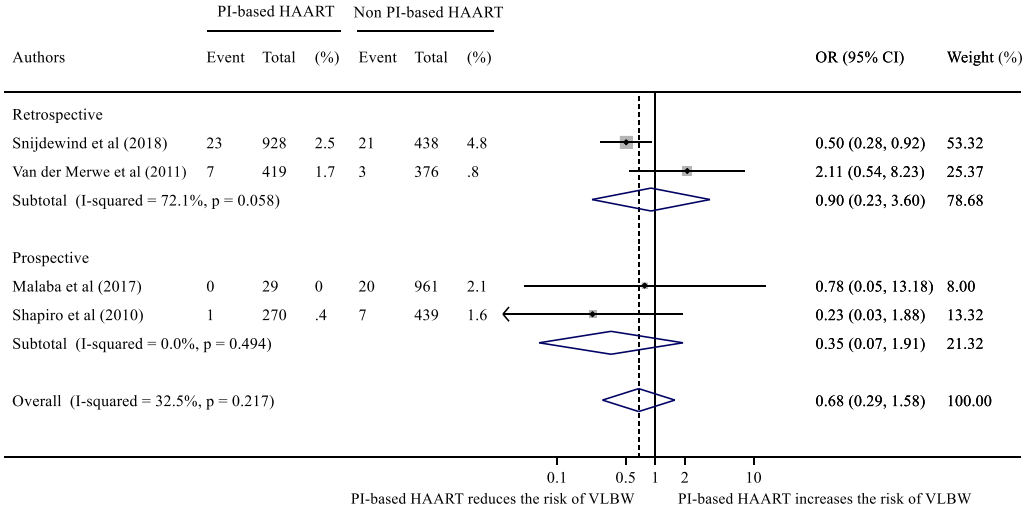


Figure 3.75. Forest plot of risk of very low birth weight in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VLBW, very low birth weight.

3.4.6.3 Effect of ART class on gestational age and birth weight combined

3.4.6.3.1 Small for gestational age (SGA)

The risk of SGA in HIV-positive pregnant women receiving PI versus those receiving non PI-based regimens was reported in 10 cohorts (seven retrospective and three prospective), including 11,462 women. Three cohorts were conducted in LMICs and seven in high-income countries (Figure 3.76). The pooled unadjusted effect estimates of these 10 cohorts showed no difference in SGA risk between PI and non PI-based regimes (pooled OR: 1.19, 95% CI: 0.92, 1.54), with moderate heterogeneity (I^2 = 68.8%) (Figure 3.76). The finding persisted across cohort

design and country-income status: retrospective (pooled OR: 1.19, 95% CI: 0.87, 1.63) and prospective (pooled OR: 1.23, 95% CI: 0.77, 1.97) (Figure 3.76A); LMIC (pooled OR: 1.53, 95% CI: 0.80, 2.91) and high-income country (pooled OR: 0.97, 95% CI: 0.82, 1.15) (Figure 3.76B). A high degree of heterogeneity was evident in retrospective (I^2 = 78.9%) and LMIC (I^2 = 84.7%), but there was none (I^2 = 0%) in prospective or high-income country (Figure 3.76).

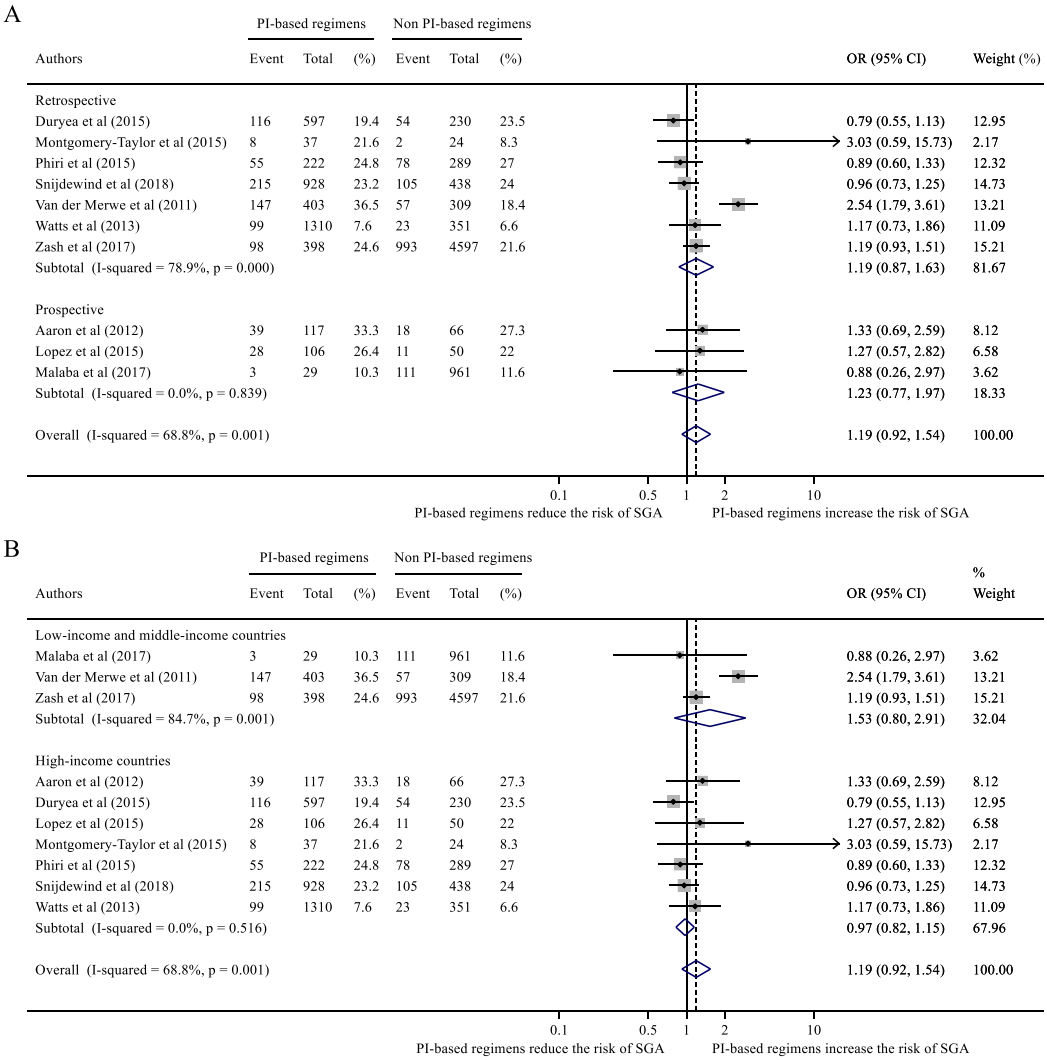


Figure 3.76. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

The contour-enhanced funnel plot in Figure 3.77 seems symmetric, suggesting no evidence of publication bias; the Harbord's test showed no evidence of small-study effects (P = 0.833).

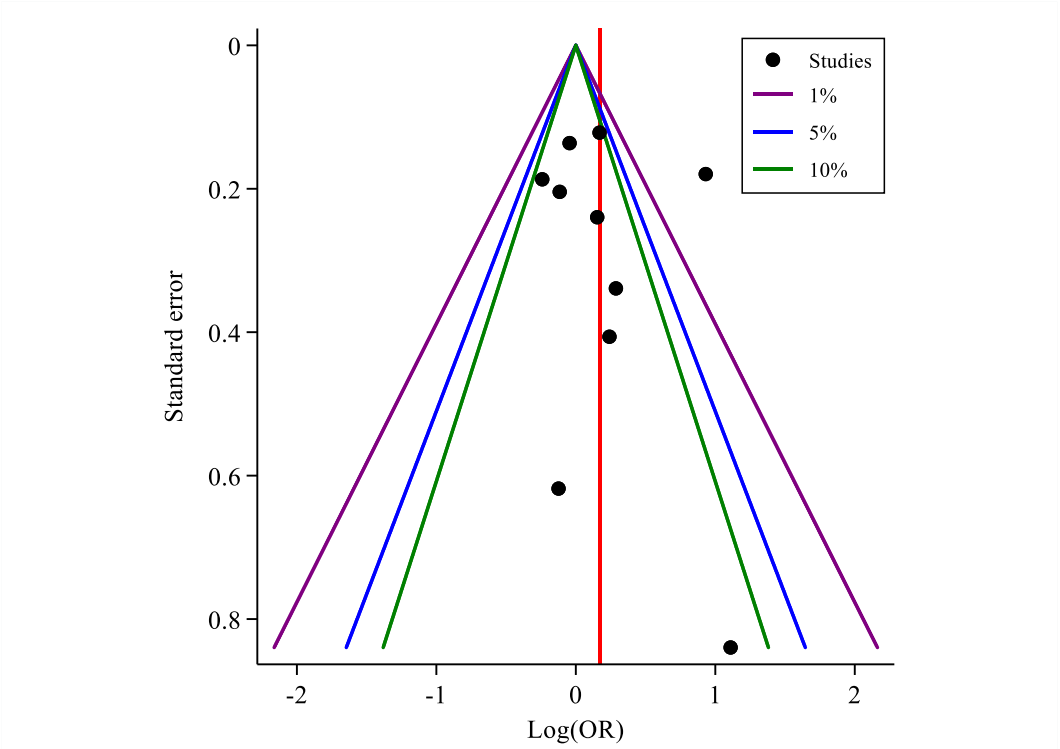


Figure 3.77. Contour-enhanced funnel plot of the 10 cohorts comparing the risk of small for gestational age in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data. Solid black circles correspond to the 10 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 10 cohorts, eight (five retrospective and three prospective) used HAART, and the pooled unadjusted effect estimates showed an association between PI-based HAART and an increased risk of SGA at borderline statistical significance (pooled OR: 1.34, 95% CI: 0.99, 1.81) (Figure 3.78). PI-based HAART was not associated with SGA in the sub-group analyses of retrospective (pooled OR: 1.40, 95% CI: 0.94, 2.07) and prospective cohorts (pooled OR: 1.23, 95% CI: 0.77,

1.97) (Figure 3.78A), nor in LMIC (pooled OR: 1.53, 95% CI: 0.80, 2.91) or high-income country (pooled OR: 1.07, 95% CI: 0.87, 1.32) (Figure 3.78B).

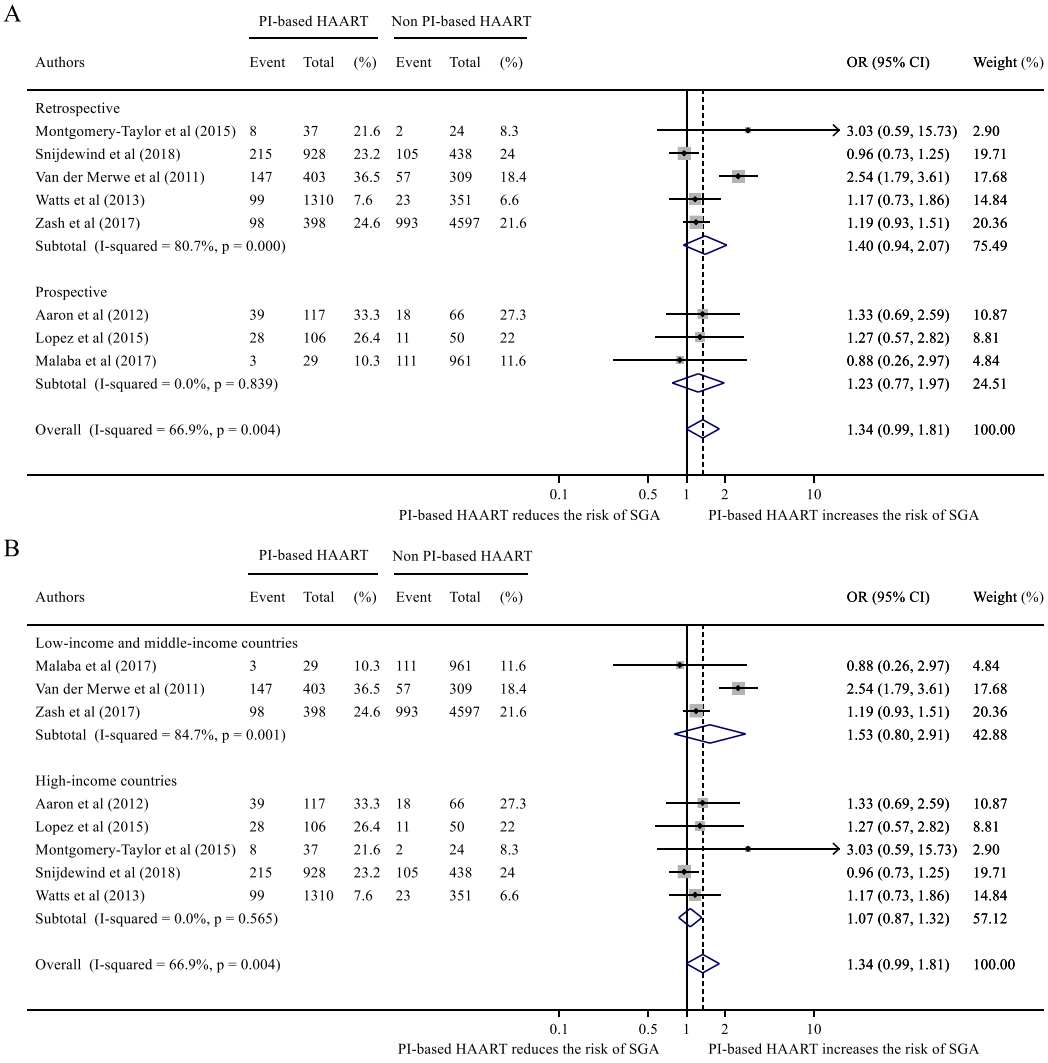


Figure 3.78. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

The meta-analysis of adjusted effect estimates including three retrospective cohorts showed no difference in SGA risk between PI and non PI-based regimens (pooled adjusted OR: 1.14, 95% CI: 0.73, 1.80) (Figure 3.79). The finding remained when the analysis was limited to women on PI and non PI-based HAART (pooled adjusted OR: 1.35, 95% CI: 0.82, 2.25) (Figure 3.79).

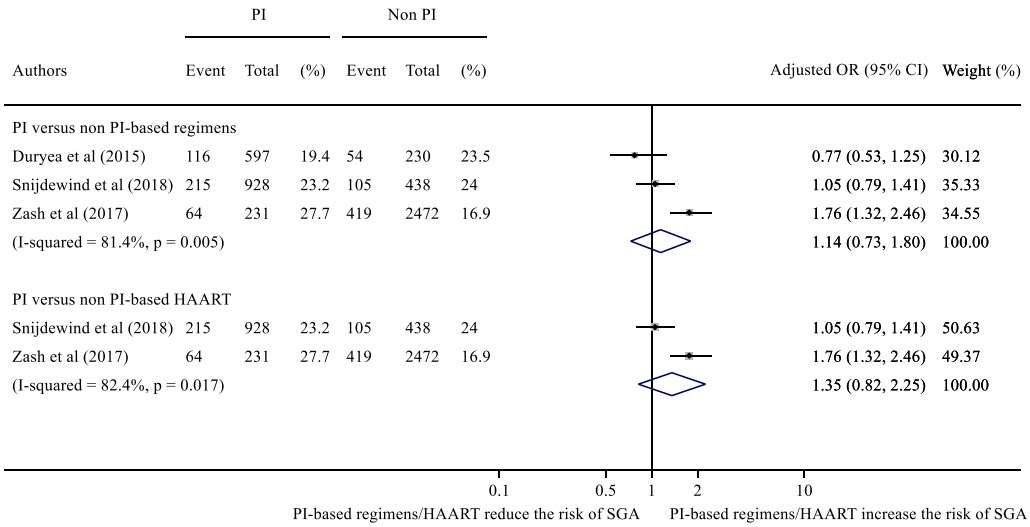


Figure 3.79. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with PI versus non PI-based regimens/HAART using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

3.4.6.3.2 Very small for gestational age (VSGA)

The meta-analysis of unadjusted effect estimates of two cohorts, including 5,178 women, showed an association between PI-based HAART and an increased risk of VSGA (pooled OR: 1.45, 95% CI: 1.08, 1.95) (Figure 3.80). Of these two cohorts, one reported an adjusted effect estimate indicating an association between PI-based HAART and an increased risk of VSGA (adjusted OR: 1.93, 95% CI: 1.29, 2.94) [96].

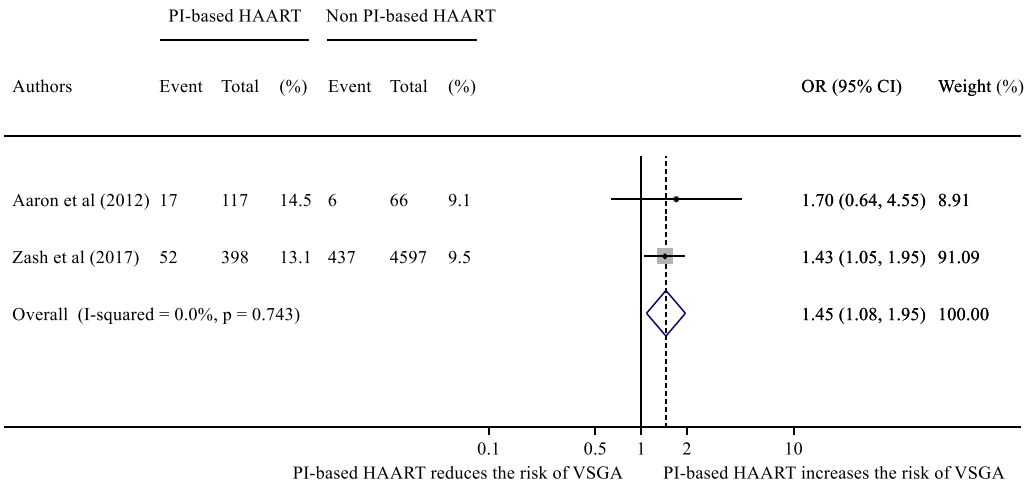


Figure 3.80. Forest plot of risk of very small for gestational age in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VSGA, very small for gestational age.

3.4.6.4 Effect of ART class on fetal and neonatal mortality

3.4.6.4.1 Stillbirth

The pooled unadjusted effect estimates of two retrospective cohorts, including 12,996 women, showed no difference in stillbirth risk between PI and non PI-based regimens (pooled OR: 1.05, 95% CI: 0.73, 1.50) (Figure 3.81). The finding persisted when the analysis was restricted to women on PI and non PI-based HAART (one study, OR: 1.13, 95% CI: 0.67, 1.91) (Figure 3.81). One of the two cohorts reported an adjusted effect estimate indicating no association between PI-based HAART and stillbirth (adjusted OR: 1.84, 95% CI: 0.94, 3.69) [96].

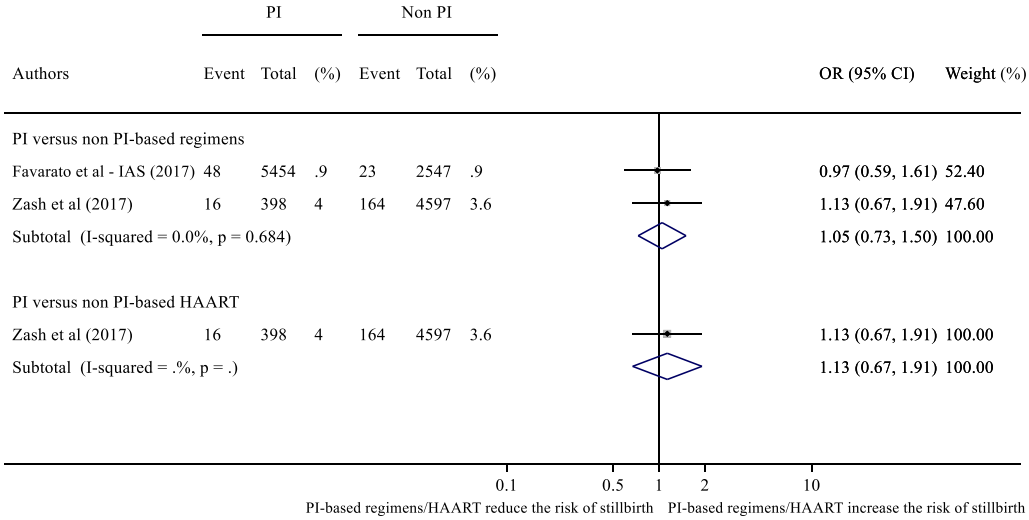


Figure 3.81. Forest plots of risk of stillbirth in HIV-positive pregnant women treated with PI versus non PI-based regimens/HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor.

3.4.6.4.2 Neonatal death (NND)

A retrospective cohort conducted in Botswana, including 4,995 women, reported no difference in NND risk between PI and non PI-based HAART: unadjusted (OR: 1.84, 95% CI: 0.97, 3.50) and adjusted association (adjusted OR: 1.61, 95% CI: 0.56, 4.73) [96].

3.4.6.5 Effect of ART class on mother-to-child transmission (MTCT)

No difference in MTCT risk between PI and non PI-based HAART was shown by the meta-analysis of unadjusted effect estimates of two cohorts conducted in LMICs, including 1,372 women, (pooled OR: 0.84, 95% CI: 0.45, 1.57) (Figure 3.82).

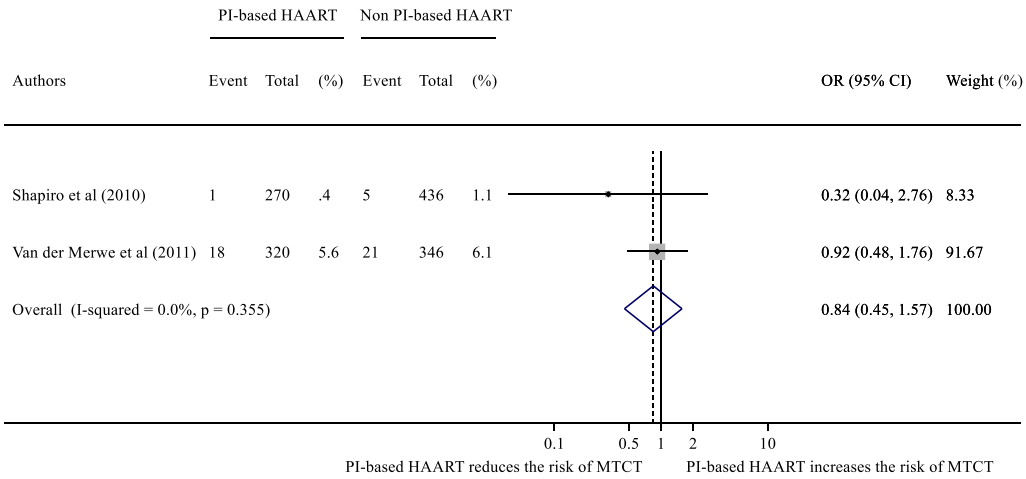


Figure 3.82. Forest plot of risk of mother-to-child transmission in HIV-positive pregnant women treated with PI versus non PI-based HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio; PI, protease inhibitor.

3.4.6.6 Summary of meta-analysis results

The summary of meta-analysis results for the effect of ART class on perinatal outcomes is provided in Appendix 3.10: Tables 3.8 and 3.9.

3.4.7 Effect of timing of ART initiation on perinatal outcomes

Pairwise meta-analyses assessing the risk of adverse perinatal outcomes in HIV-positive pregnant women with different timings of ART initiation were conducted. The exposure group was women initiating ART pre-conception, and comparator group was women initiating post-conception. Among women initiating ART post-conception, the exposure group was those initiating ART in the first trimester, and comparator group was those initiating after the first trimester of pregnancy.

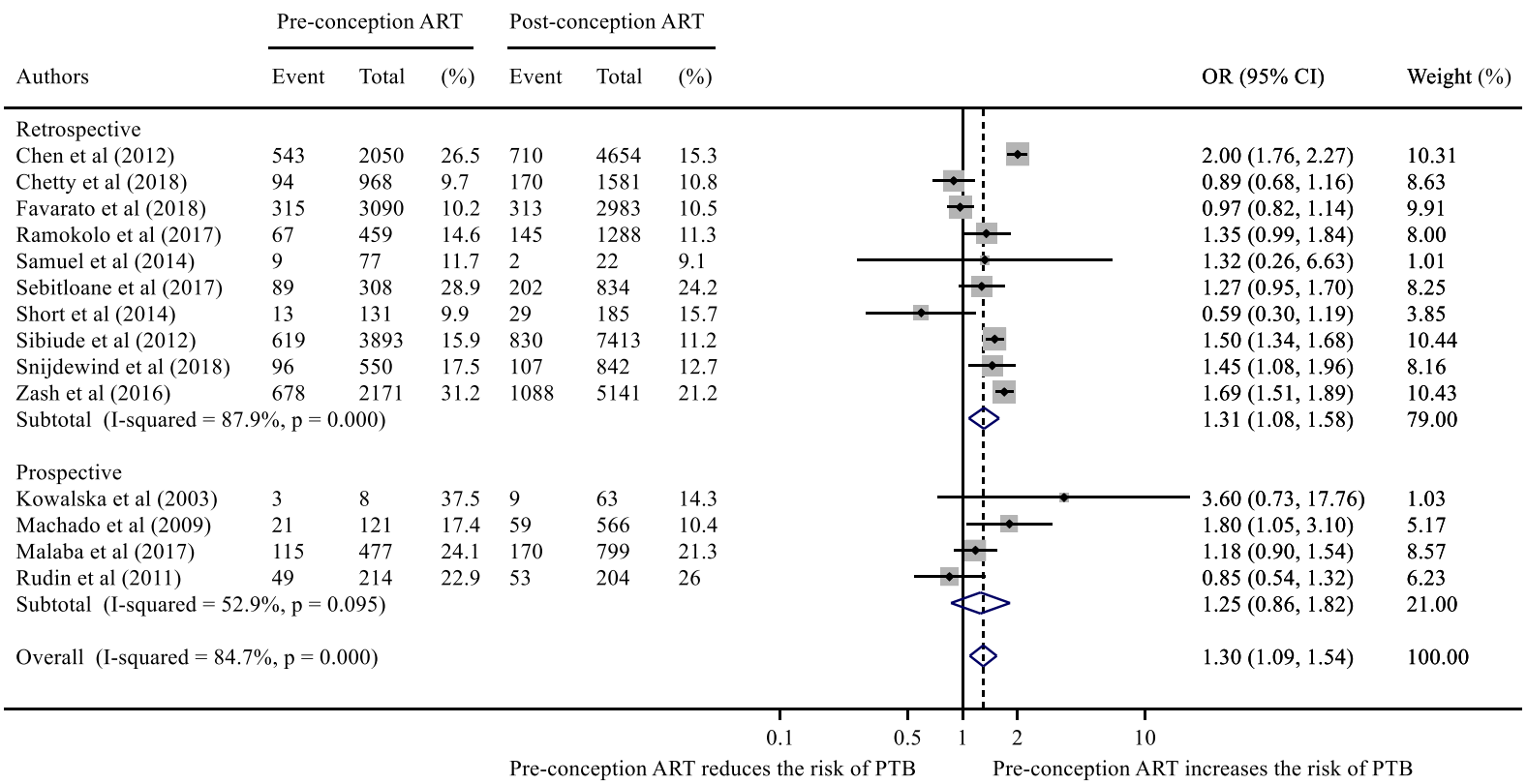
3.4.7.1 Effect of timing of ART initiation on gestational age at delivery

3.4.7.1.1 Preterm birth (PTB)

Pre-conception versus post-conception

The risk of PTB in women initiating ART pre-conception versus those initiating post-conception was reported in 14 cohorts (10 retrospective and four prospective) including 41,092 women; seven cohorts were conducted in LMICs and seven in high-income countries. The pooled unadjusted effect estimates showed that pre-conception initiation was associated with an increased risk of PTB compared with post-conception initiation (pooled OR: 1.30, 95% CI: 1.09, 1.54), with a high degree of heterogeneity (I^2 = 84.7%) (Figure 3.83). The finding persisted in the sub-group analysis of retrospective (pooled OR: 1.31, 95% CI: 1.08, 1.58), but not prospective cohorts (pooled OR: 1.25, 95% CI: 0.86, 1.82) (Figure 3.83A), and in the sub-group analysis of cohorts conducted in LMICs (pooled OR: 1.41, 95% CI: 1.14, 1.75), but not in high-income countries (pooled OR: 1.14, 95% CI: 0.86, 1.51) (Figure 3.83B).

A


Pre-conception ART
Post-conception ART
Authors
Event
Total
(%)
Event
Total
(%)
OR (95% CI)
Weight (%)
Retrospective
Chen et al (2012) 543 2050 26.5 710 4654 15.3 2.00 (1.76, 2.27) 10.31
Chetty et al (2018) 94 968 9.7 170 1581 10.8 0.89 (0.68, 1.16) 8.63
Favarato et al (2018) 315 3090 10.2 313 2983 10.5 0.97 (0.82, 1.14) 9.91
Ramokolo et al (2017) 67 459 14.6 145 1288 11.3 1.35 (0.99, 1.84) 8.00
Samuel et al (2014) 9 77 11.7 2 22 9.1 1.32 (0.26, 6.63) 1.01
Sebitloane et al (2017) 89 308 28.9 202 834 24.2 1.27 (0.95, 1.70) 8.25
Short et al (2014) 13 131 9.9 29 185 15.7 0.59 (0.30, 1.19) 3.85
Sibiude et al (2012) 619 3893 15.9 830 7413 11.2 1.50 (1.34, 1.68) 10.44
Snijdewind et al (2018) 96 550 17.5 107 842 12.7 1.45 (1.08, 1.96) 8.16
Zash et al (2016) 678 2171 31.2 1088 5141 21.2 1.69 (1.51, 1.89) 10.43
Subtotal (I-squared = 87.9%, p = 0.000) 1.31 (1.08, 1.58) 79.00
Prospective
Kowalska et al (2003) 3 8 37.5 9 63 14.3 3.60 (0.73, 17.76) 1.03
Machado et al (2009) 21 121 17.4 59 566 10.4 1.80 (1.05, 3.10) 5.17
Malaba et al (2017) 115 477 24.1 170 799 21.3 1.18 (0.90, 1.54) 8.57
Rudin et al (2011) 49 214 22.9 53 204 26 0.85 (0.54, 1.32) 6.23
Subtotal (I-squared = 52.9%, p = 0.095) 1.25 (0.86, 1.82) 21.00
Overall (I-squared = 84.7%, p = 0.000) 1.30 (1.09, 1.54) 100.00
0.1
0.5
1
2
10
Pre-conception ART reduces the risk of PTB
Pre-conception ART increases the risk of PTB

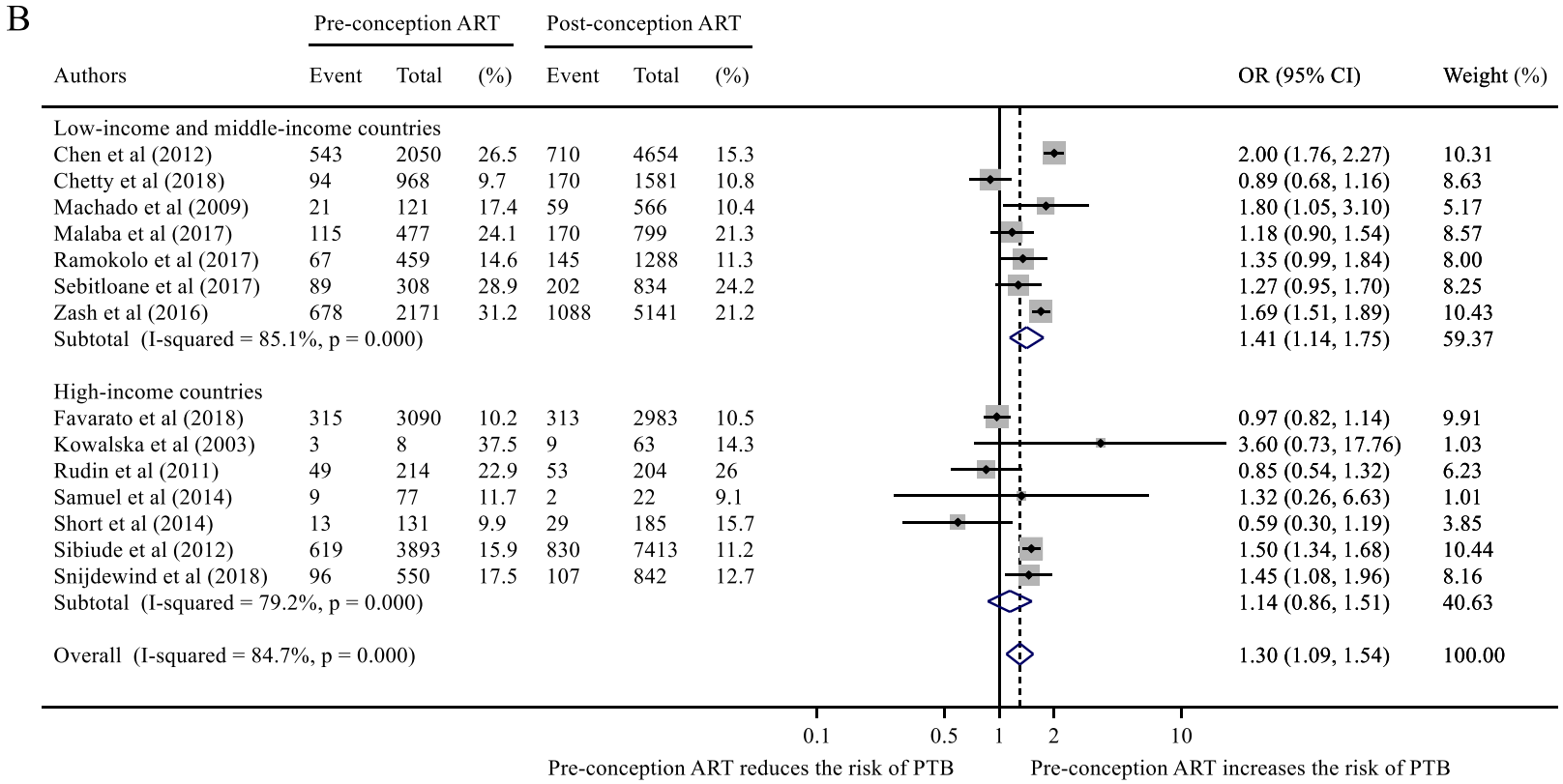


Figure 3.83. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

The contour-enhanced funnel plot in Figure 3.84 seems symmetric, suggesting no evidence of publication bias; the Harbord's test showed no evidence of small-study effects (P = 0.214).

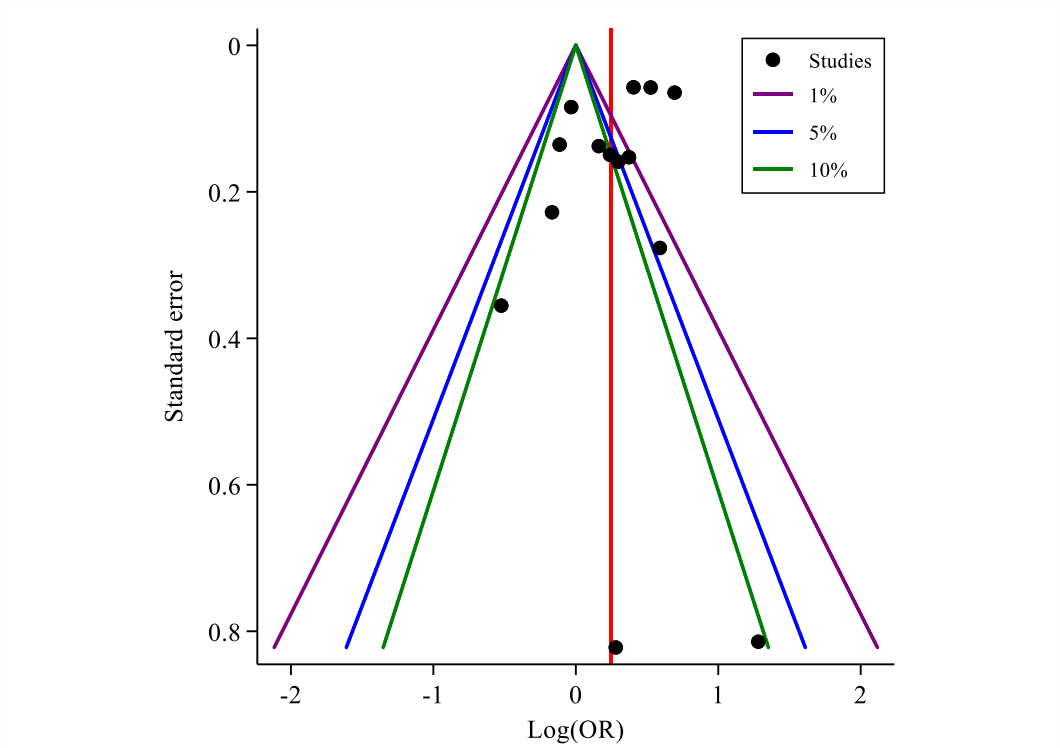


Figure 3.84. Contour-enhanced funnel plot of the 14 cohorts comparing the risk of preterm birth in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data. Solid black circles correspond to the 14 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Of the 14 cohorts, 13 specified ART complexity: two used both non HAART and HAART and 11 used HAART only (Appendix 3.11: Figure 3.51 and Figure 3.52). Pre-conception initiation was associated with an increased risk of PTB in women receiving HAART (pooled OR: 1.22, 95% CI: 1.01, 1.47) (Appendix 3.11: Figure 3.52), but not non-HAART (pooled OR: 0.49, 95% CI: 0.09, 2.70) (Appendix 3.11: Figure 3.51). Ten cohorts specified ART class: five used both non PI and PI-

based HAART, four used non PI, and one PI-based HAART only (Appendix 3.11: Figure 3.53 and Figure 3.54). The association between pre-conception initiation and an increased risk of PTB was observed in women receiving non PI (pooled OR: 1.28, 95% CI: 1.05, 1.56) (Appendix 3.11: Figure 3.53), and PI-based HAART at borderline statistical significance (pooled OR: 1.54, 95% CI: 0.99, 2.41) (Appendix 3.11: Figure 3.54).

The meta-analysis of adjusted effect estimates, including seven cohorts, showed an association between pre-conception initiation of ART and an increased risk of PTB (pooled adjusted OR: 1.37, 95% CI: 1.23, 1.54), with no heterogeneity (I^2 = 4.7%) (Figure 3.85). The finding persisted in the sub-group analysis of retrospective (pooled adjusted OR: 1.35, 95% CI: 1.21, 1.51), but not prospective cohorts (pooled adjusted OR: 2.36, 95% CI: 0.70, 7.91) (Figure 3.85A). The finding persisted across country-income status: LMIC (pooled adjusted OR: 1.60, 95% CI: 1.22, 2.09) and high-income country (pooled adjusted OR: 1.31, 95% CI: 1.15, 1.48) (Figure 3.85B). All these findings remained when the analyses were restricted to the six cohorts that used HAART (Appendix 3.11: Figure 3.55).

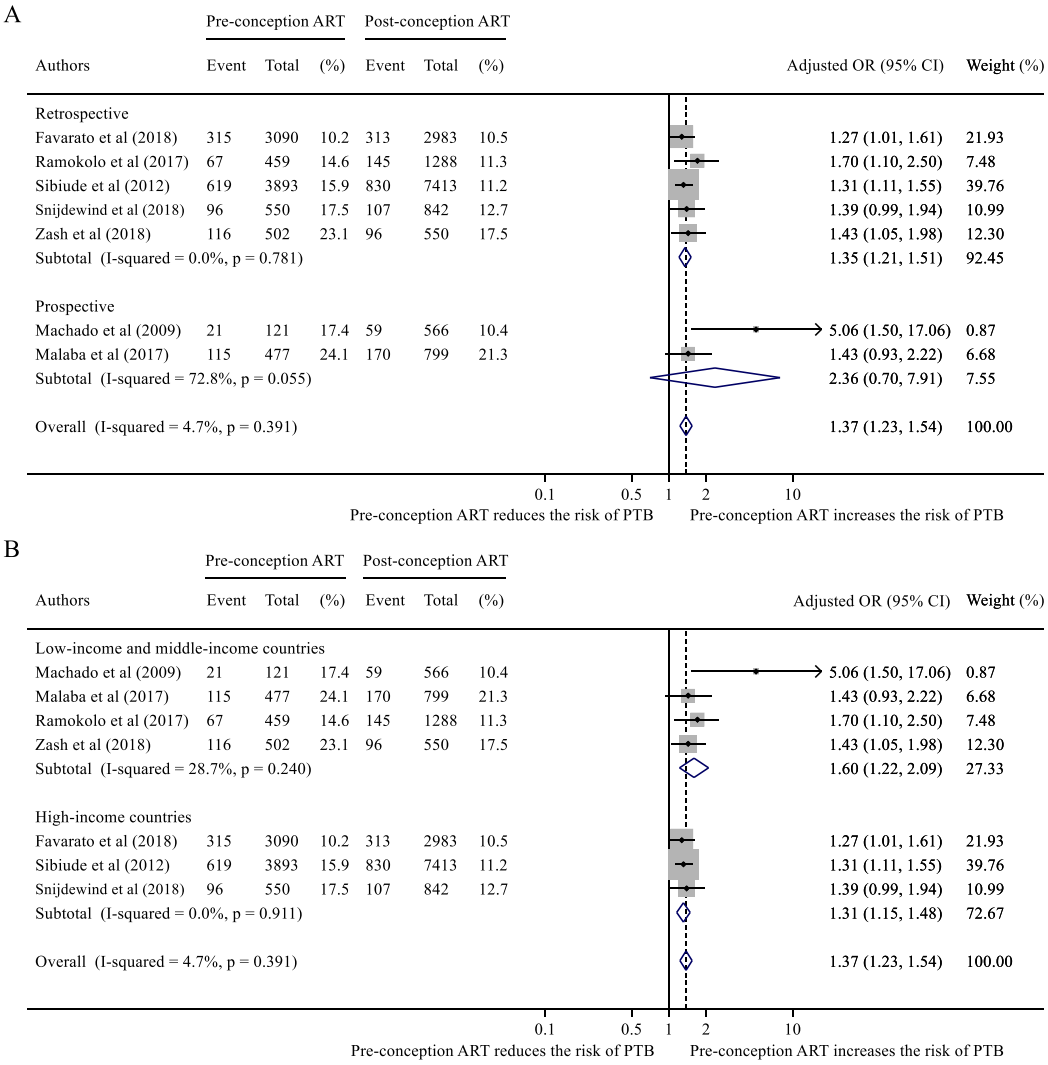


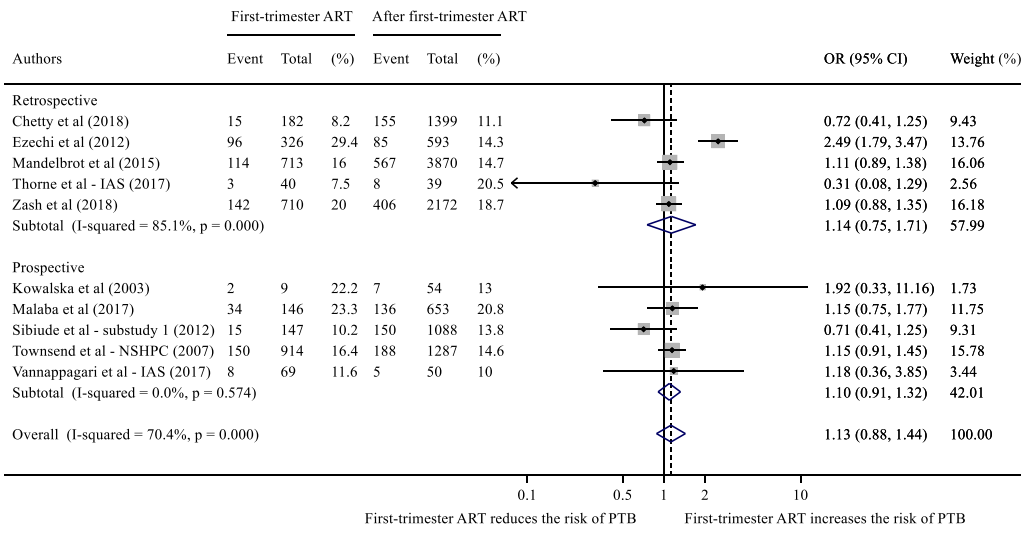
Figure 3.85. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using adjusted effect estimates, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

First trimester versus after first trimester

Ten cohorts (five retrospective and five prospective), including 14,461 women, reported the risk of PTB in women starting ART in the first trimester versus those starting after the first trimester; four cohorts were conducted in LMICs, five in high-income countries and one in multi-regions (Figure 3.86). The pooled

uandjusted effect estimates of these 10 cohorts revealed no difference in PTB risk between first trimester and after first trimester initiation of ART (pooled OR: 1.13, 95% CI: 0.88, 1.44), with moderate heterogeneity (I^2 = 70.4%) (Figure 3.86A). The finding was consistently observed across cohort design and country-income status: retrospecive (pooled OR: 1.14, 95% CI: 0.75, 1.71) and prospective (pooled OR: 1.10, 95% CI: 0.91, 1.32) (Figure 3.86A); LMIC (pooled OR: 1.26, 95% CI: 0.77, 2.03) and high-income country (pooled OR: 1.04, 95% CI: 0.83, 1.30) (Figure 3.86B). A high degree of heterogeneity was observed in retrospective (I^2 = 85.1%) and LMIC (I^2 = 86.5%), but no heterogeneity (I^2 = 0%) in prospective, and low heterogeneity in high-income country (I^2 = 31.2%) (Figure 3.86).

A



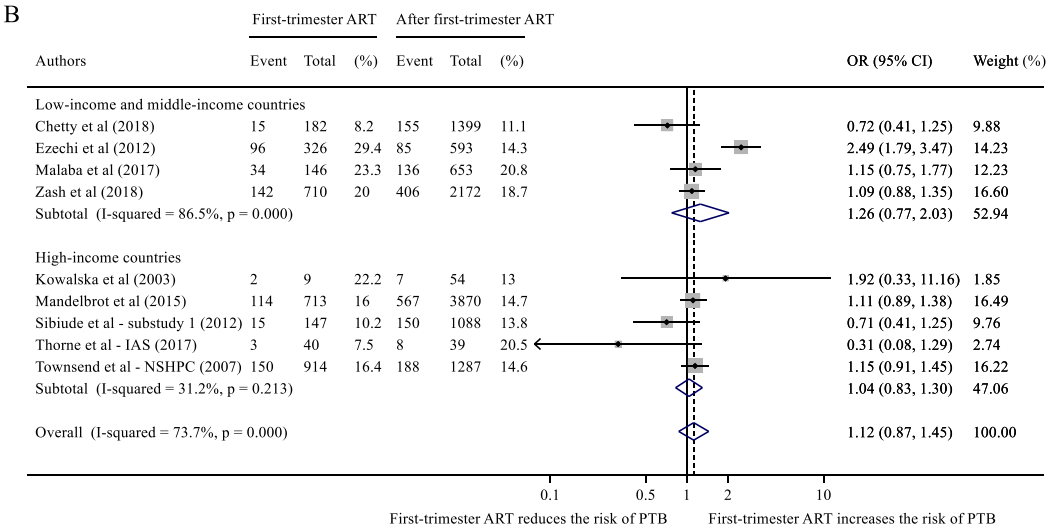


Figure 3.86. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Figure 3.87 shows a symmetric contour-enhanced funnel plot, indicating no evidence of publication bias; the Harbord's test had a *P* value of 0.668, indicating no evidence of small-study effects.

Of the 10 cohorts, six (two retrospective and four prospective) used HAART; when the analyses were restricted to these six cohorts, the findings were similar to the above results: no difference in PTB risk between first trimester and after first trimester initiation of HAART in the overall analysis (pooled OR: 1.28, 95% CI: 0.91, 1.81) (Appendix 3.11: Figure 3.56); in retrospective (pooled OR: 1.63, 95% CI: 0.72, 3.68) and prospective cohorts (pooled OR: 1.08, 95% CI: 0.79, 1.46) (Appendix 3.11: Figure 3.56A), and in LMIC (pooled OR: 1.46, 95% CI: 0.85, 2.51) and high-income country (pooled OR: 1.06, 95% CI: 0.61, 1.84) (Appendix 3.11: Figure 3.56B).

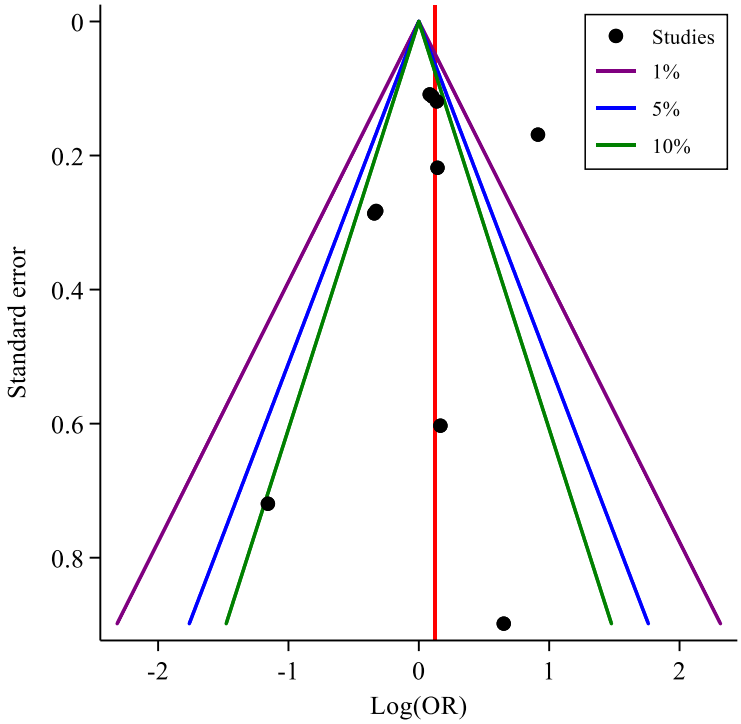


Figure 3.87. Contour-enhanced funnel plot of the 10 cohorts comparing the risk of preterm birth in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using unadjusted data. Solid black circles correspond to the 10 cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

The meta-analysis of adjusted effect estimates of four cohorts showed no difference in PTB risk between first trimester and after first trimester initiation of ART (pooled adjusted OR: 1.52, 95% CI: 0.73, 3.17); a high degree of heterogeneity (I^2 = 94%) was observed (Figure 3.88). Sub-group analyses by cohort design and by country-income status were not performed because only one study, conducted in high-income countries, was prospective [381]. Of the four cohorts reporting adjusted effect estimates, three used HAART; when the analysis was restricted to these three cohorts, the finding was similar to the above results: no difference in PTB risk between first trimester and after first trimester initiation of HAART (pooled adjusted OR: 1.86, 95% CI: 0.77, 4.48) (Appendix 3.11: Figure 3.57).

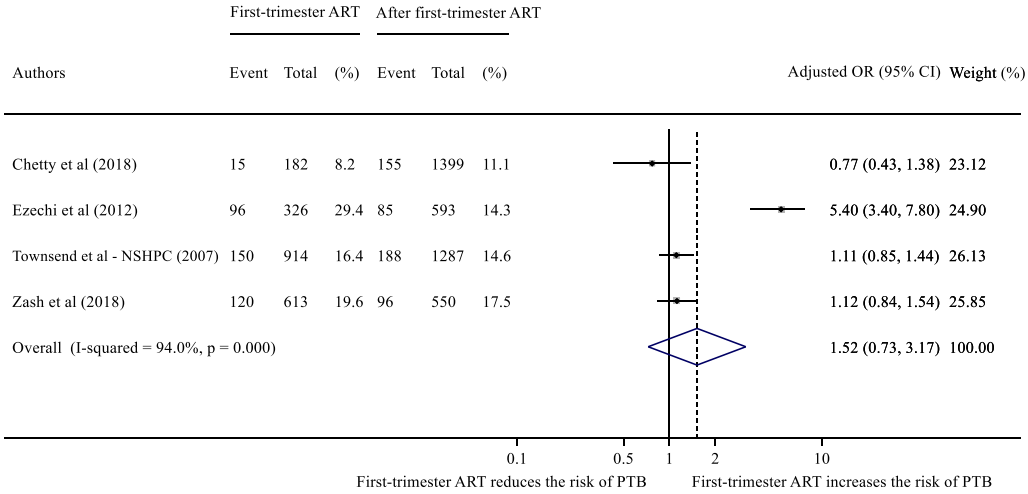


Figure 3.88. Forest plot of risk of preterm birth in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

A prospective cohort conducted in South Africa, including 779 women, reported adjusted effect estimates showing no difference in PTB risk between first trimester and first half of second trimester (adjusted OR: 1.10, 95% CI: 0.63, 1.92), second half of second trimester (adjusted OR: 1.27, 95% CI: 0.70, 2.27) and third trimester (adjusted OR: 0.71, 95% CI: 0.40, 1.27) initiation of HAART [29].

3.4.7.1.2 Spontaneous preterm birth (sPTB)

A retrospective cohort conducted in Nigeria, including 919 women, showed a higher risk of sPTB in women initiating HAART in the first trimester than those initiating after first trimester: unadjusted (OR: 2.49, 95% CI: 1.79, 3.47) and adjusted association (adjusted OR: 5.40, 95% CI: 3.40, 7.80) [398].

3.4.7.1.3 Very preterm birth (VPTB)

Pre-conception versus post-conception

The meta-analysis of unadjusted effect estimates of four cohorts (three retrospective and one prospective), including 14,730 women, showed that pre-conception was associated with an increased risk of VPTB compared with post-conception initiation of ART (pooled OR: 1.32, 95% CI: 1.01, 1.73); low heterogeneity (I^2 = 30.2%) was observed (Figure 3.89). The finding remained in the sub-group analysis of cohorts conducted in high-income countries (pooled OR: 1.49, 95% CI: 1.19, 1.85) but not in LMICs (pooled OR: 1.00, 95% CI: 0.68, 1.47) (Figure 3.89). Sub-group analysis by cohort design was not performed because only one of the four cohorts was prospective [29].

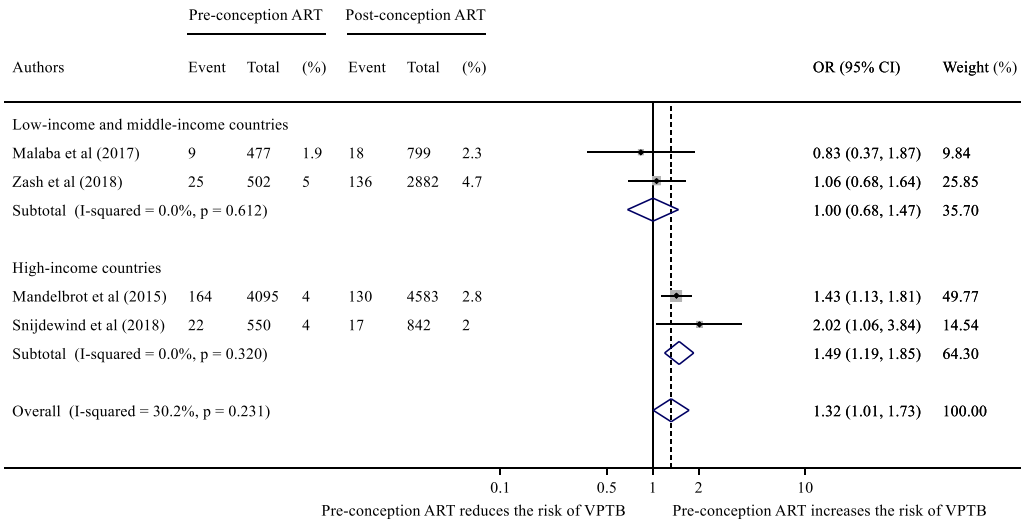


Figure 3.89. Forest plot of risk of very preterm birth in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data, by country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VPTB, very preterm birth.

Of the four cohorts, three used HAART, and the pooled unadjusted effect estimates showed no association between pre-conception and VPTB compared with post-conception initiation of HAART (pooled OR: 1.23, 95% CI: 0.76, 1.97) (Figure 3.90A). Of these three cohorts, two reported adjusted effect estimates; the meta-analysis of these two cohorts revealed that pre-conception initiation of HAART remained not associated with VPTB (pooled adjusted OR: 1.28, 95% CI: 0.92, 1.77) (Figure 3.90B).

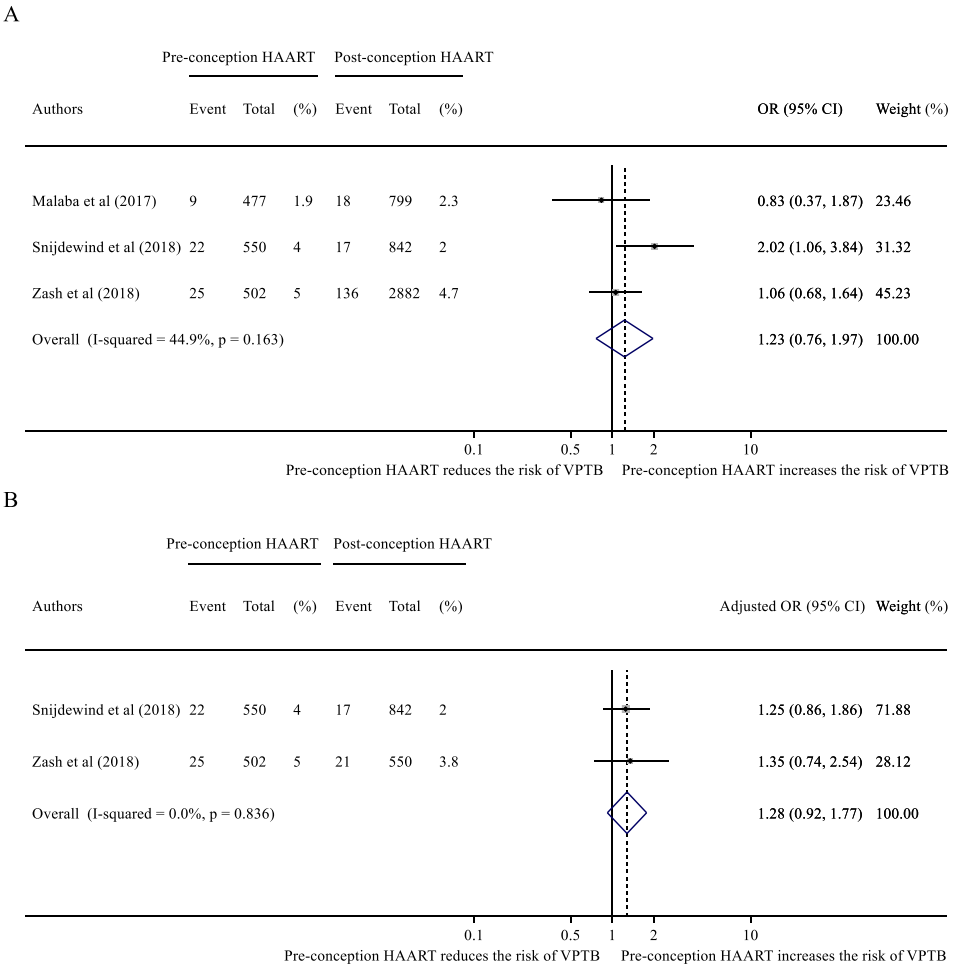
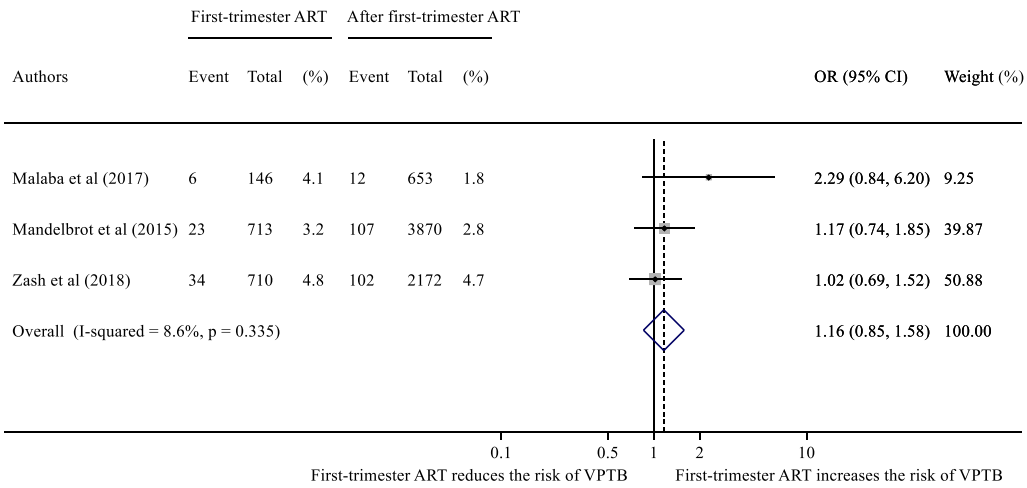


Figure 3.90. Forest plots of risk of very preterm birth in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted (A) and adjusted effect estimates (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VPTB, very preterm birth.

First trimester versus after first trimester

The pooled unadjusted effect estimates of three cohorts, including 8,264 women, showed no difference in VPTB risk between first trimester and after first trimester initiation of ART (pooled OR: 1.16, 95% CI: 0.85, 1.58) (Figure 3.91A). The finding remained when the analysis was restricted to the two cohorts that used HAART (pooled OR: 1.34, 95% CI: 0.63, 2.82) (Figure 3.91B). Of these two cohorts, one reported an adjusted effect estimate suggesting no difference in VPTB risk between first trimester and after first trimester initiation of HAART (adjusted OR: 1.24, 95% CI: 0.69, 2.28) [404].

A



B

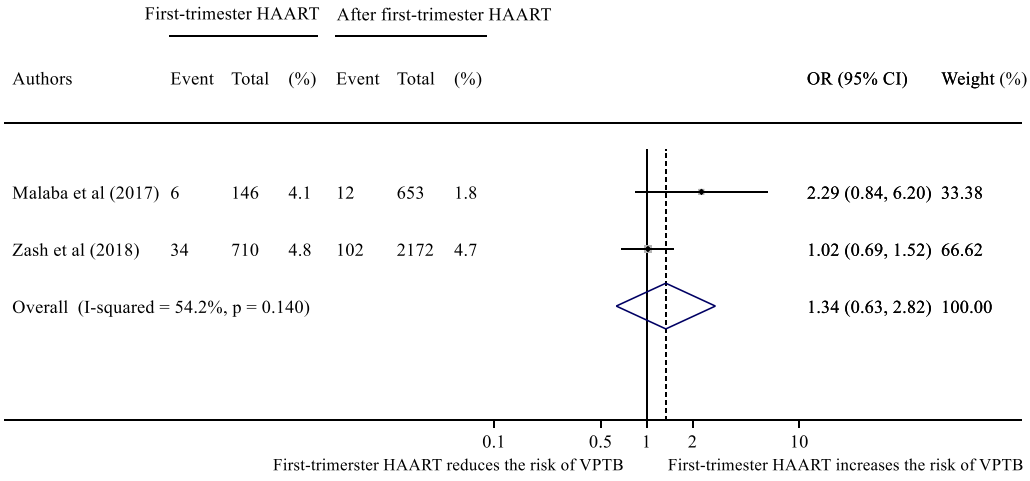


Figure 3.91. Forest plots of risk of very preterm birth in HIV-positive pregnant women who initiated treatment in the first trimester versus after first trimester using unadjusted data: treated with any ART (A) or HAART (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VPTB, very preterm birth.

3.4.7.2 Effect of timing of ART initiation on birth weight

3.4.7.2.1 Low birth weight (LBW)

Pre-conception versus post-conception

The risk of LBW in women with pre-conception versus those with post-conception initiation of ART was reported in eight cohorts (five retrospective and three prospective), including 9,729 women. Five cohorts were conducted in LMICs and three in high-income countries (Figure 3.92). The synthesis of unadjusted effect estimates of these eight cohorts showed no difference in LBW risk between pre-conception and post-conception initiation of ART (pooled OR: 1.17, 95% CI: 0.87, 1.59), with moderate heterogeneity (I^2 = 72.5%) (Figure 3.92). The finding persisted across cohort design and country-income status: retrospective (pooled OR: 0.98, 95% CI: 0.69, 1.38) and prospective (pooled OR: 1.64, 95% CI: 0.88, 3.05) (Figure 3.92A); LMIC (pooled OR: 1.22, 95% CI: 0.88, 1.70) and high-income country (pooled OR: 0.54, 95% CI: 0.12, 2.46) (Figure 3.92B).

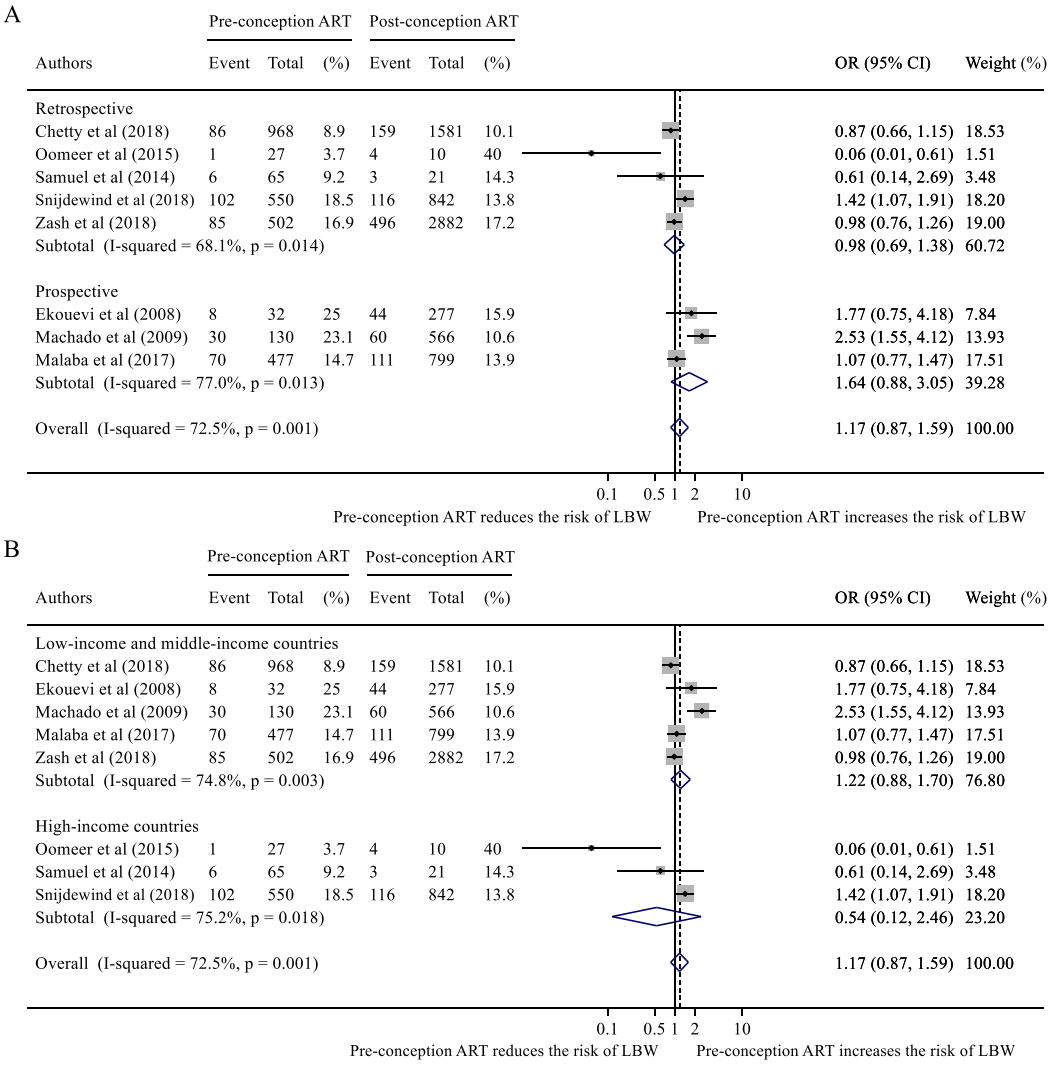


Figure 3.92. Forest plots of risk of low birth weight in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

Of the eight cohorts, seven used HAART; the meta-analyses showed similar findings to the above results: 1) no difference in LBW risk between pre-conception and post-conception initiation of HAART in the overall meta-analysis (pooled OR: 1.15, 95% CI: 0.88, 1.50) (Appendix 3.11: Figure 3.58); 2) the finding was consistently observed across cohort design and country-income

status: retrospective (pooled OR: 1.02, 95% CI: 0.76, 1.37) and prospective (pooled OR: 1.51, 95% CI: 0.79, 2.89) (Appendix 3.11: Figure 3.58A), LMIC (pooled OR: 1.12, 95% CI: 0.82, 1.53) and high-income country (pooled OR: 1.29, 95% CI: 0.76, 2.20) (Appendix 3.11: Figure 3.58B).

Of the seven cohorts that used HAART, five (three retrospective and two prospective) reported adjusted effect estimates. The meta-analysis of these five cohorts revealed no association between pre-conception initiation of HAART and LBW (pooled adjusted OR: 1.32, 95% CI: 0.95, 1.83), with moderate heterogeneity (I^2 = 64.3%) (Figure 3.93). The finding remained irrespective of cohort design: retrospective (pooled adjusted OR: 1.11, 95% CI: 0.89, 1.38) and prospective (pooled adjusted OR: 2.15, 95% CI: 0.85, 5.44) (Figure 3.93). Sub-group analysis by country-income status was not performed because only one of the five cohorts was conducted in a high-income country [417].

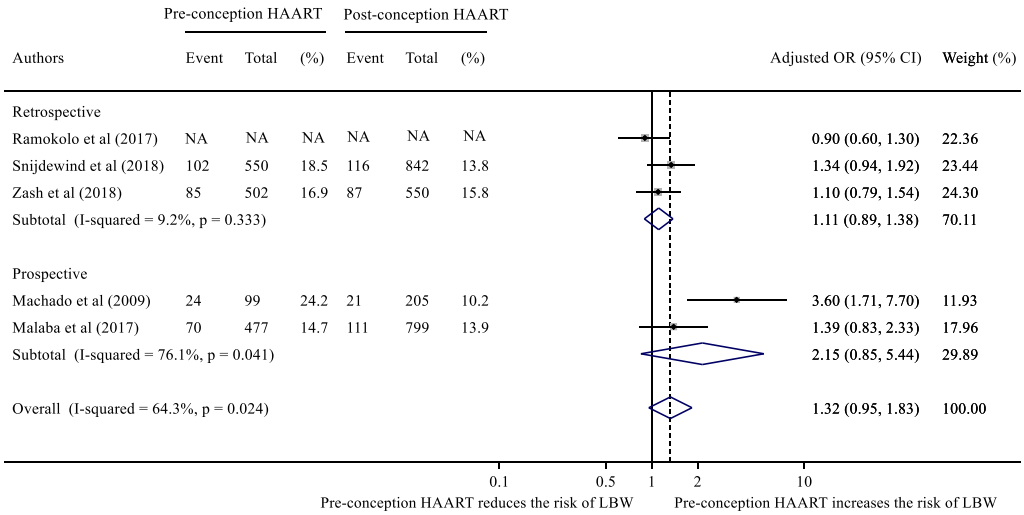


Figure 3.93. Forest plot of risk of low birth weight in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using adjusted effect estimates, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; NA. not available; OR, odds ratio.

First trimester versus after first trimester

The pooled unadjusted effect estimates of four cohorts (two retrospective and two prospective), including 3,877 women, showed no difference in LBW risk between first trimester and after first trimester initiation of ART (pooled OR: 1.09, 95% CI: 0.73, 1.61); low heterogeneity (I^2 = 44.7%) was evident (Figure 3.94). The finding was consistently observed across cohort design: retrospective (pooled OR: 0.74, 95% CI: 0.31, 1.81) and prospective (pooled OR: 1.51, 95% CI: 0.97, 2.34) (Figure 3.94). Sub-group analysis by country-income status was not performed because only one of the four cohorts was conducted in high-income countries [418].

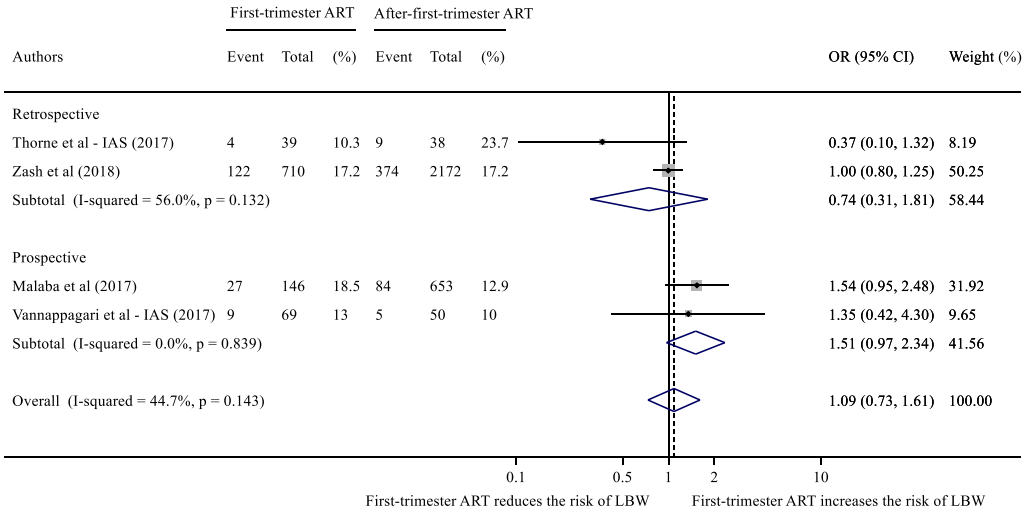


Figure 3.94. Forest plot of risk of low birth weight in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

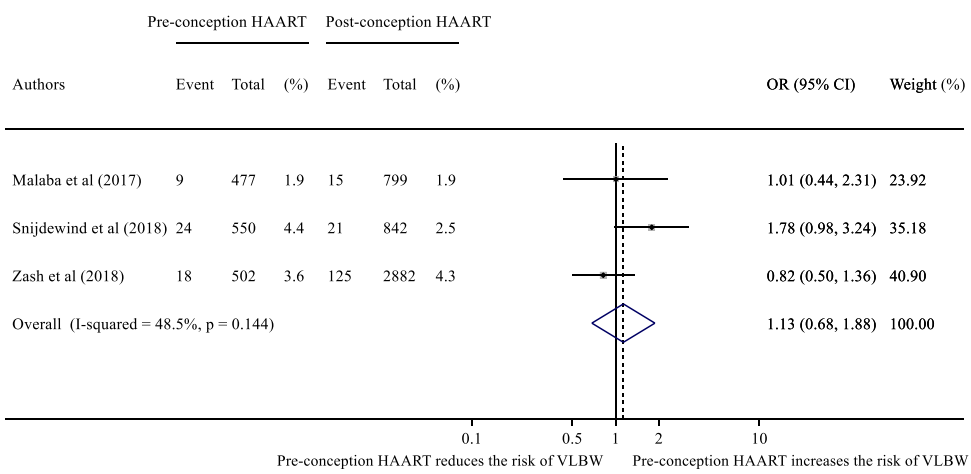
Of the four cohorts, two used HAART; the meta-analysis showed no association between first trimester initiation of HAART and LBW (pooled OR: 1.17, 95% CI: 0.78, 1.77) (Appendix 3.11: Figure 3.59). These two cohorts reported adjusted effect estimates: the first cohort [404] showed no difference in LBW risk between first trimester and after first trimester (adjusted OR: 1.02, 95% CI: 0.75, 1.42); the second cohort [29] showed no difference in LBW risk between first trimester and first half of second trimester (adjusted OR: 1.43, 95% CI: 0.74, 2.78), second half of second trimester (adjusted OR: 1.47, 95% CI: 0.75, 2.94), or third trimester (adjusted OR: 0.87, 95% CI: 0.44, 1.69) initiation of HAART.

3.4.7.2.2 Very low birth weight (VLBW)

Pre-conception versus post-conception

The synthesis of unadjusted effect estimates of three cohorts, including 6,052 women all of whom were on HAART, showed no association between pre-conception initiation and VLBW (pooled OR: 1.13, 95% CI: 0.68, 1.88) (Figure 3.95A). The finding remained in the meta-analysis of adjusted effect estimates including two cohorts (pooled adjusted OR: 1.01, 95% CI: 0.62, 1.65) (Figure 3.95B).

A



B

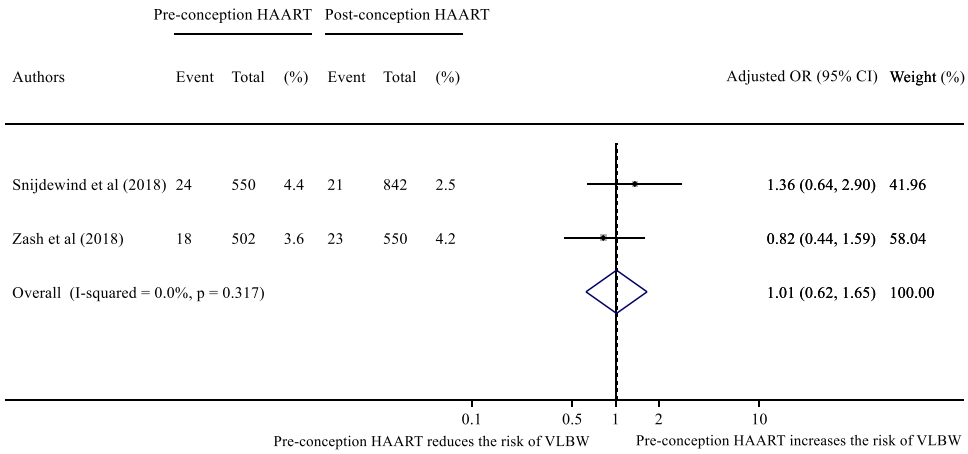


Figure 3.95. Forest plots of risk of very low birth weight in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted (A) and adjusted effect estimates (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VLBW, very low birth weight.

First trimester versus after first trimester

The synthesis of unadjusted effect estimates of three cohorts, including 3,800 women, showed no difference in VLBW risk between first trimester and after first trimester initiation of ART (pooled OR: 1.07, 95% CI: 0.73, 1.56) (Figure 3.96). The finding remained when the analysis was restricted to the two cohorts that used HAART (pooled OR: 1.07, 95% CI: 0.72, 1.58) (Figure 3.96). Of these, one reported an adjusted effect estimate showing no difference in VLBW risk between first trimester and after first trimester initiation of HAART (adjusted OR: 0.98, 95% CI: 0.55, 1.76) [404].

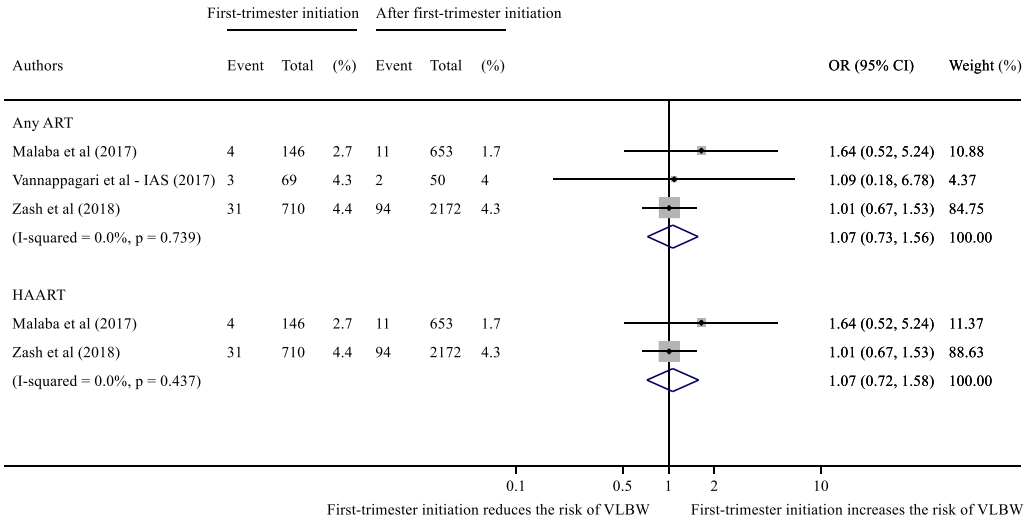


Figure 3.96. Forest plots of risk of very low birth weight in HIV-positive pregnant women who initiated any ART/HAART in the first trimester versus after first trimester using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VLBW, very low birth weight.

3.4.7.3 Effect of timing of ART initiation on gestational age and birth weight combined

3.4.7.3.1 Small for gestational age (SGA)

Pre-conception versus post-conception

The risk of SGA in HIV-positive pregnant women starting ART pre-conception versus those starting post-conception was reported in eight cohorts (five prospective and three retrospective), including 15,936 women. Four cohorts were conducted in LMICs and four in high-income countries (Figure 3.97). The meta-analysis of unadjusted effect estimates including these eight cohorts revealed no association between pre-conception initiation of ART and SGA, compared with post-conception initiation of ART (pooled OR: 1.08, 95% CI: 0.90, 1.28); low heterogeneity (I^2 = 46.3%) was observed (Figure 3.97A and Figure 3.97B). The

finding persisted irrespective of country-income status: LMIC (pooled OR: 1.09, 95% CI: 0.89, 1.34) and high-income country (pooled OR: 0.89, 95% CI: 0.53, 1.50) (Figure 3.97B). However, sub-group analysis by cohort design showed an association between pre-conception initiation of ART and an increased risk of SGA in retrospective (pooled OR: 1.20, 95% CI: 1.04, 1.39), but not prospective cohorts (pooled OR: 0.83, 95% CI: 0.62, 1.12) (Figure 3.97A).

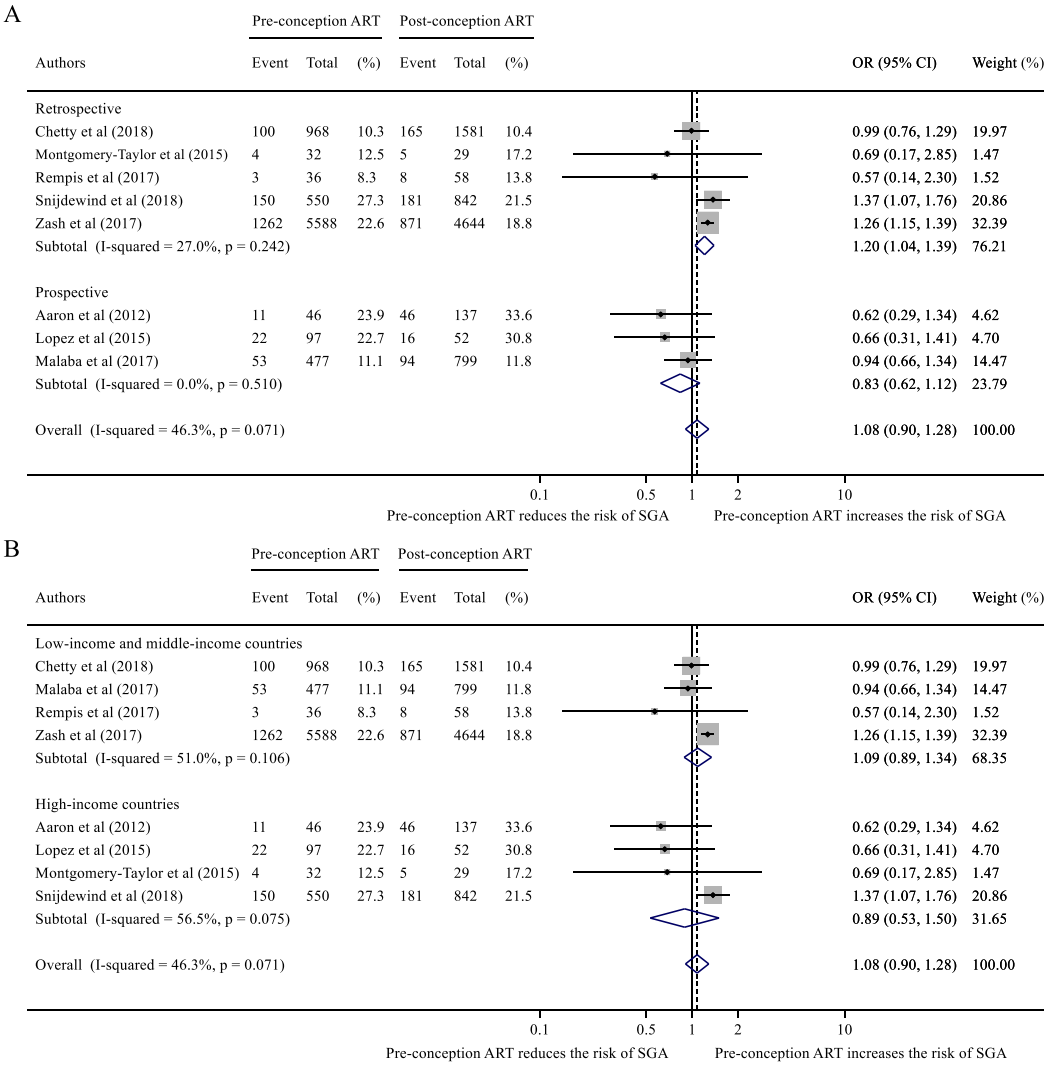


Figure 3.97. Forest plots of risk of small for gestational age in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

When the analyses were restricted to women on HAART, the findings were similar to the above results: 1) no association between pre-conception initiation of HAART and SGA in the overall meta-analysis (pooled OR: 1.08, 95% CI: 0.91, 1.29) (Appendix 3.11: Figure 3.60A and Figure 3.60B); 2) the finding remained across country-income status: LMIC (pooled OR: 1.10, 95% CI: 0.90, 1.34) and high-income country (pooled OR: 0.89, 95% CI: 0.53, 1.50) (Appendix 3.11: Figure 3.60B); 3) an association between pre-conception initiation of HAART and an increased risk of SGA in retrospective (pooled OR: 1.22, 95% CI: 1.08, 1.39), but not prospective cohorts (pooled OR: 0.83, 95% CI: 0.62, 1.12) (Appendix 3.11: Figure 3.60A).

The pooled adjusted effect estimates including five cohorts (four retrospective and one prospective) showed an increased risk of SGA in women initiating HAART pre-conception compared with those initiating post-conception (pooled adjusted OR: 1.27, 95% CI: 1.14, 1.42), with no heterogeneity (I^2 = 15.5%) (Figure 3.98). Of the five cohorts, only one study was prospective [29] and one study was conducted in a high-income country [90], therefore sub-group analyses by cohort design and by country-income status were not performed.

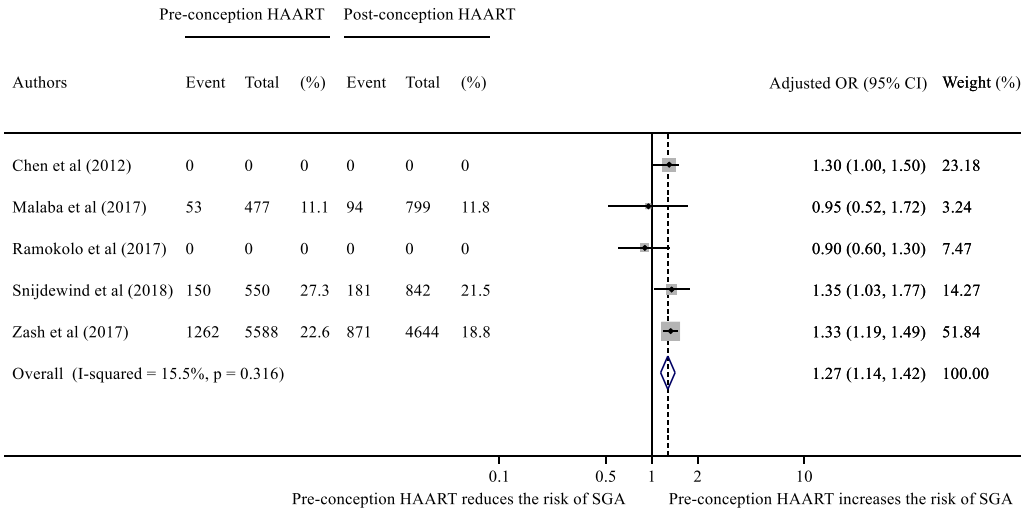


Figure 3.98. Forest plot of risk of small for gestational age in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; OR, odds ratio; SGA, small for gestational age.

First trimester versus after first trimester

The synthesis of unadjusted effect estimates of five cohorts (three retrospective and two prospective), including 6,029 women, showed no difference in SGA risk between first trimester and after first trimester initiation of ART (pooled OR: 1.04, 95% CI: 0.87, 1.24), with no heterogeneity (I^2 = 0%) (Figure 3.99). The finding remained irrespective of cohort design and country-income status: retrospective (pooled OR: 1.01, 95% CI: 0.84, 1.22) and prospective (pooled OR: 1.10, 95% CI: 0.55, 2.21) (Figure 3.99A); LMIC (pooled OR: 1.09, 95% CI: 0.90, 1.31) and high-income country (pooled OR: 0.79, 95% CI: 0.51, 1.24) (Figure 3.99B).

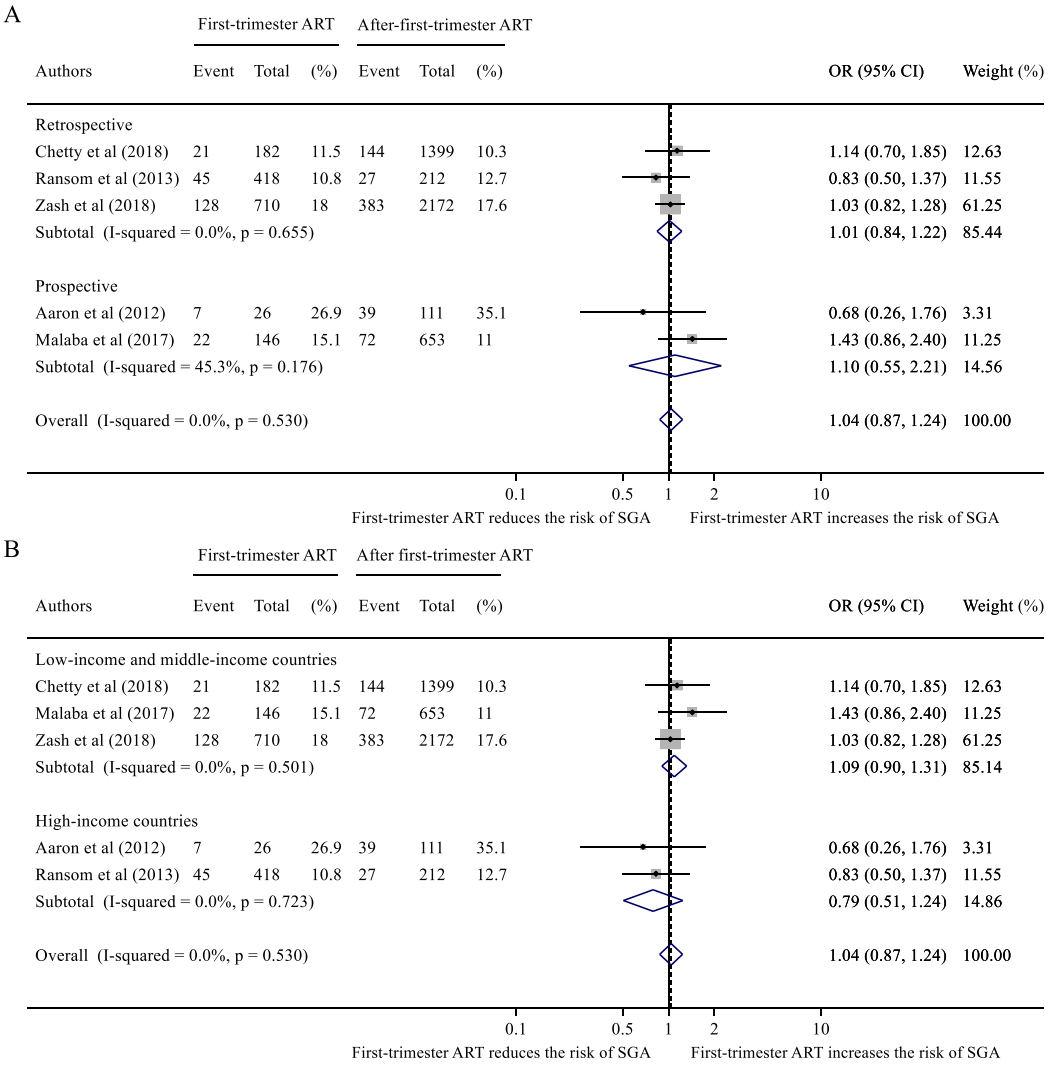


Figure 3.99. Forest plots of risk of small for gestational age in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

When the analyses were restricted to the four cohorts (two retrospective and two prospective) that used HAART, the results were similar to the above findings: 1) no association between first trimester initiation of HAART and SGA in the overall meta-analysis (pooled OR: 1.03, 95% CI: 0.85, 1.24) (Appendix 3.11: Figure

3.61); 2) the finding was consistently observed across cohort design and country-income status: retrospective (pooled OR: 0.99, 95% CI: 0.81, 1.22) and prospective (pooled OR: 1.10, 95% CI: 0.55, 2.21) (Appendix 3.11: Figure 3.61A); LMIC (pooled OR: 1.11, 95% CI: 0.84, 1.47) and high-income country (pooled OR: 0.79, 95% CI: 0.51, 1.24) (Appendix 3.11: Figure 3.61B).

The meta-analysis of adjusted effect estimates including two retrospective cohorts conducted in LMICs showed no difference in SGA risk between first trimester and after first trimester initiation of ART (pooled adjusted OR: 1.06, 95% CI: 0.81, 1.40) (Figure 3.100). The adjusted effect estimates of a prospective cohort from South Africa showed no difference in SGA risk between first trimester and first half of second trimester (adjusted OR: 1.30, 95% CI: 0.64, 2.63), second half of second trimester (adjusted OR: 1.35, 95% CI: 0.65, 2.86), and third trimester (adjusted OR: 0.62, 95% CI: 0.30, 1.27) initiation of HAART [29].

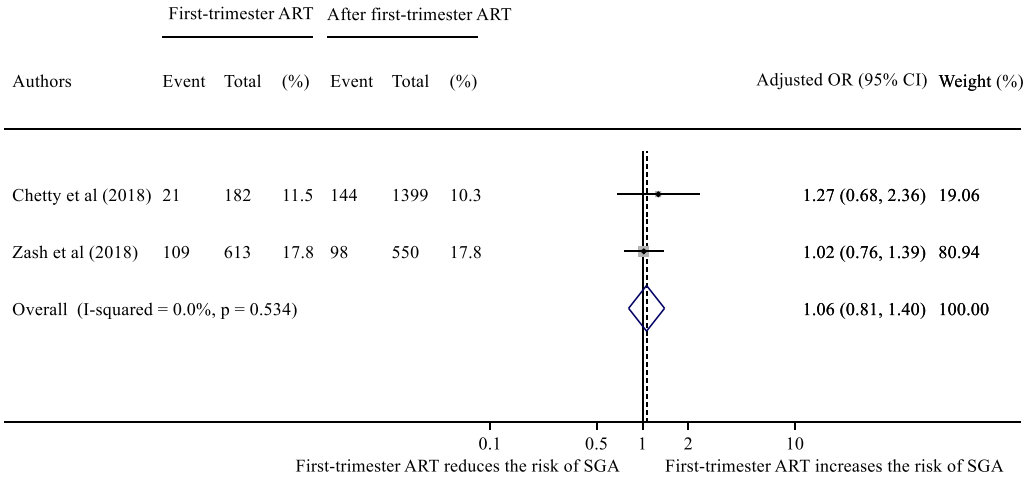


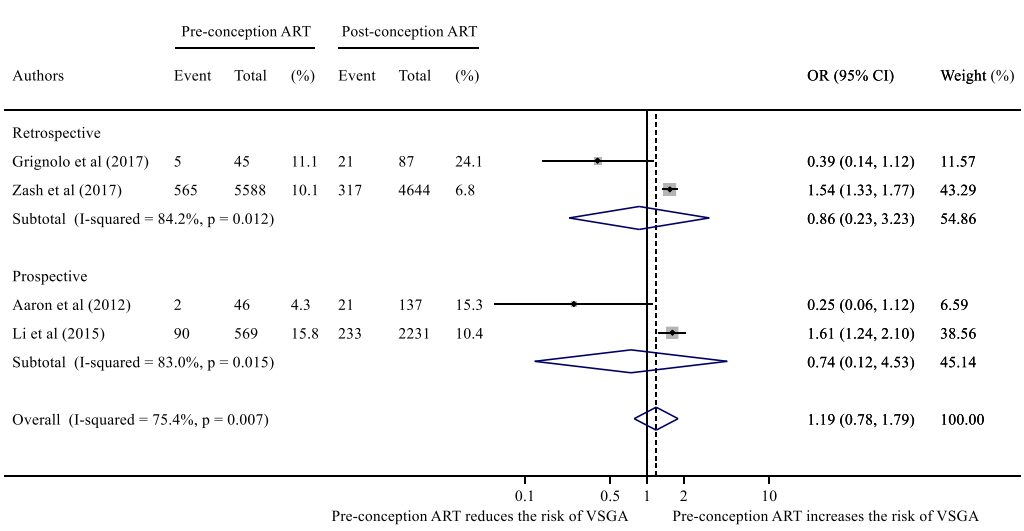
Figure 3.100. Forest plot of risk of small for gestational age in HIV-positive pregnant women who initiated ART in the first trimester versus after first trimester using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

3.4.7.3.2 Very small for gestational age (VSGA)

Pre-conception versus post-conception

The meta-analysis of unadjusted effect estimates of four cohorts (two retrospective and two prospective), including 13,347 women, revealed no association between pre-conception initiation of ART and VSGA (pooled OR: 1.19, 95% CI: 0.78, 1.79), with a high degree of heterogeneity (I^2 = 75.4%) (Figure 3.101). The finding persisted across cohort design: retrospective (pooled OR: 0.86, 95% CI: 0.23, 3.23) and prospective (pooled OR: 0.74, 95% CI: 0.12, 4.53) (Figure 3.101A). In LMICs, pre-conception initiation of ART was associated with an increased risk of VSGA (pooled OR: 1.55, 95% CI: 1.37, 1.76); however, in high-income countries, pre-conception initiation of ART was associated with a decreased risk of VSGA (pooled OR: 0.34, 95% CI: 0.14, 0.80) (Figure 3.101B).

A



B

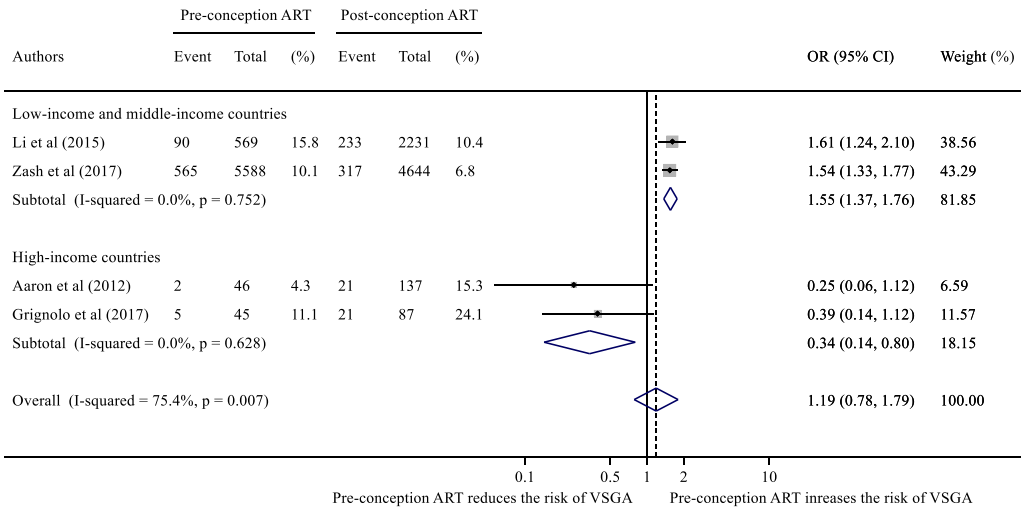


Figure 3.101. Forest plots of risk of very small for gestational age in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

Of the four cohorts, three used HAART. The synthesis of these three cohorts showed no association between pre-conception initiation of HAART and VSGA (pooled OR: 1.15, 95% CI: 0.73, 1.84) (Appendix 3.11: Figure 3.62).

The meta-analysis of adjusted effect estimates, including two retrospective cohorts, showed no difference in VSGA risk between pre-conception and post-conception initiation of HAART (pooled adjusted OR: 0.93, 95% CI: 0.25, 3.47) (Figure 3.102).

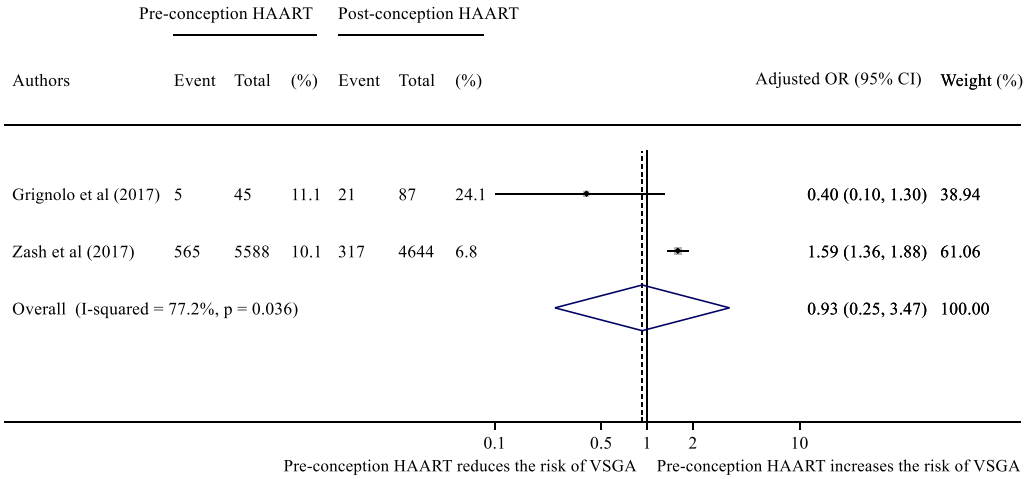


Figure 3.102. Forest plot of risk of very small for gestational age in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

First trimester versus after first trimester

No difference in VSGA risk between first trimester and after first trimester initiation of HAART (pooled OR: 0.86, 95% CI: 0.61, 1.22) was seen in the meta-analysis of unajdusted effect estimates of two cohorts, including 3,019 women (Figure 3.103). One of these two cohorts reported an adjusted effect estimate suggesting no association between first trimester initiation of HAART and VSGA (adjusted OR: 0.71, 95% CI: 0.45, 1.14) [404].

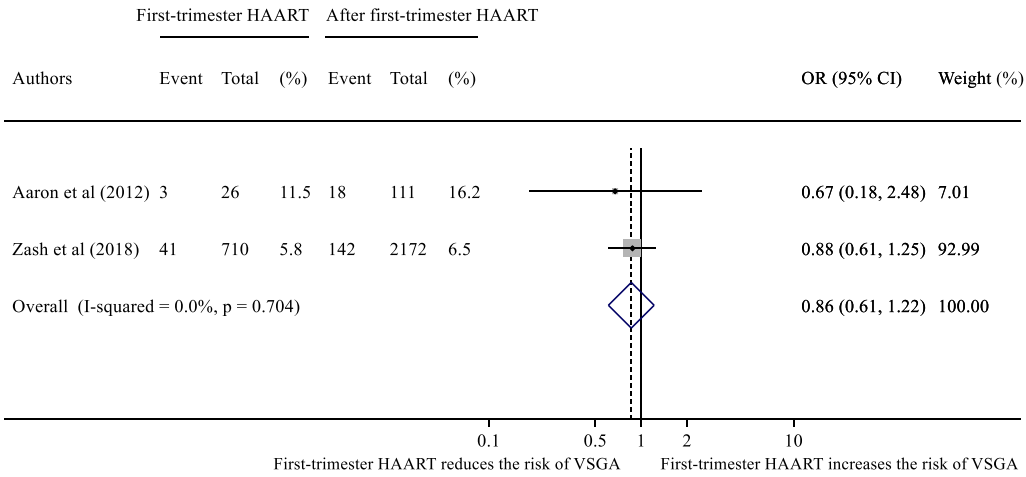


Figure 3.103. Forest plot of risk of very small for gestational age in HIV-positive pregnant women who initiated HAART in the first trimester versus after first trimester using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

3.4.7.4 Effect of timing of ART initiation on fetal and neonatal mortality

3.4.7.4.1 Stillbirth

Pre-conception versus post-conception

The synthesis of unadjusted effect estimates of two retrospective cohorts, including 17,263 women, showed no difference in the risk of stillbirth between pre-conception and post-conception initiation of ART (pooled OR: 1.38, 95% CI: 0.49, 3.85) (Figure 3.104). A retrospective cohort conducted in Botswana reported an adjusted effect estimate suggesting no association between pre-conception initiation of HAART and stillbirth (adjusted OR: 1.34, 95% CI: 0.64, 2.79) [404].

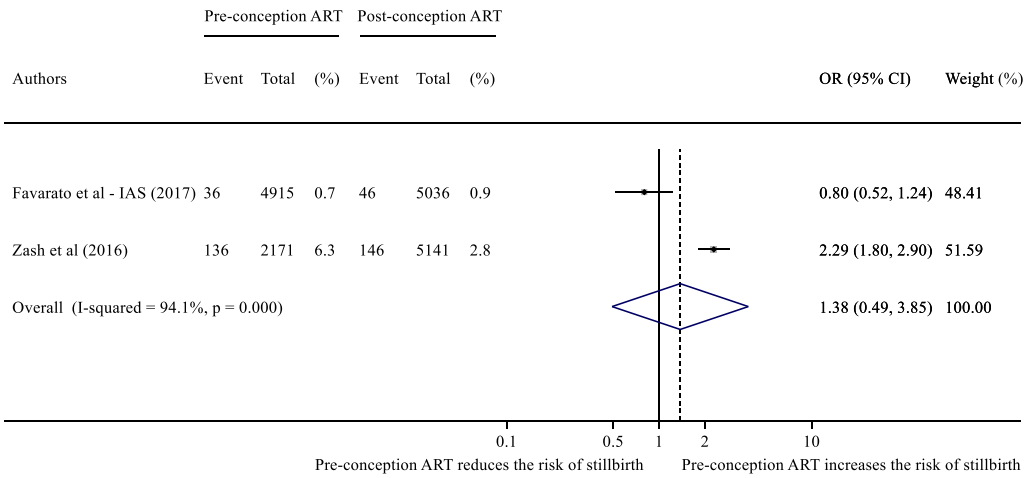


Figure 3.104. Forest plot of risk of stillbirth in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

First trimester versus after first trimester

A retrospective cohort conducted in Botswana, including 2,882 women, showed no difference in stillbirth risk between first trimester and after first trimester initiation of HAART: unadjusted (OR: 0.90, 95% CI: 0.53, 1.53), adjusted association (adjusted OR: 0.86, 95% CI: 0.40, 1.83) [404].

3.4.7.4.2 Neonatal death (NND)

Pre-conception versus post-conception

A retrospective cohort conducted in Botswana, including 10,061 women, reported unadjusted (OR: 1.27, 95% CI: 0.92, 1.77) and adjusted (adjusted OR: 1.26, 95% CI: 0.89, 1.78) effect estimates suggesting no association between pre-conception initiation of HAART and NND [96].

First trimester versus after first trimester

No association between first trimester initiation of HAART and NND was seen in a retrospective cohort conducted in Botswana, including 2,882 women: unadjusted (OR: 1.54, 95% CI: 0.87, 2.74) and adjusted effect estimate (adjusted OR: 1.76, 95% CI: 0.75, 4.27) [404].

3.4.7.5 Effect of timing of ART initiation on mother-to-child transmission (MTCT)

Pre-conception versus post-conception

The meta-analysis of unadjusted effect estimates of two retrospective cohorts conducted in high-income countries, including 8,168 women, showed an association between pre-conception initiation of ART and a reduced risk of MTCT (pooled OR: 0.20, 95% CI: 0.05, 0.83) compared with post-conception initiation of ART (Figure 3.105).

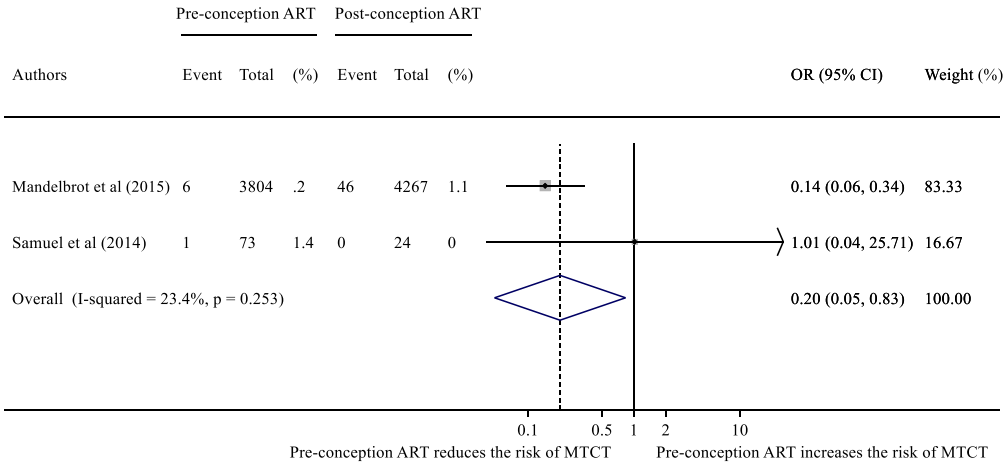


Figure 3.105. Forest plot of risk of mother-to-child transmission in HIV-positive pregnant women who initiated ART pre-conception versus post-conception using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

First trimester versus after first trimester

Of the two retrospective cohorts (Figure 3.105), one showed no difference in MTCT risk between first trimester and after first trimester initiation of ART (OR: 0.38, 95% CI: 0.12, 1.23) [152].

3.4.7.6 Summary of meta-analysis results

The summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes is provided in Appendix 3.11: Tables 3.10 and 3.11.

3.5 Discussion

This chapter aimed to explore the effects of maternal HIV/ART, antenatal ART, different ART complexity and class, and different timing of ART initiation on perinatal outcomes.

3.5.1 Effect of maternal HIV/ART on perinatal outcomes

The meta-analyses of unadjusted effect estimates showed that treated HIV-positive pregnant women are at increased risk of PTB, sPTB, VPTB, LBW and SGA compared with HIV-negative pregnant women. In sub-group analyses, overall, the associations were more consistent in retrospective cohorts and in studies conducted in high-income countries. In sensitivity analyses, the associations were strongest in HIV-positive women receiving PI-based regimens and in women initiating ART pre-conception. In the meta-analyses of adjusted effect estimates, the associations between treated maternal HIV infection and an increased risk of PTB and sPTB remained.

To my knowledge, this is the first systematic review and meta-analysis assessing the risk of adverse perinatal outcomes in HIV-positive women on ART versus HIV-negative women. Antenatal ART should improve overall maternal health, as indicated by an increased CD4 count, suppressed viral load and low risk of opportunistic infections, which should thereby reduce the risk of adverse perinatal outcomes in HIV-positive women. However, the present meta-analysis has shown that adverse perinatal outcomes remained significantly more common in HIV-positive women receiving ART than in HIV-negative women. This suggests that ART might itself have contributed to an increased risk of adverse perinatal

outcomes. The mechanisms by which ART may affect perinatal outcomes remain elusive, but include a reversal of the normal pattern of a T helper cell 1 (Th1) to T helper cell 2 (Th2) shift [431]; decreased progesterone concentrations [425], and disruption of the normal changes in the placental vasculature leading to poor placentation, placental insufficiency and preeclampsia [432]. Furthermore, the present findings also suggest that treated HIV-positive women might have more risk factors (other than HIV and ART) for adverse perinatal outcomes compared to HIV-negative women. Several studies included in the present systematic review showed that treated HIV-positive women were older [29,96,400]; less educated [29,96,399,400]; more likely to be single or unmarried [96,400,402]; more likely to smoke or use illicit drugs [96,423], and have a history of adverse perinatal outcomes [29,400,411,422], sexually transmitted infections [356], pregnancy complications [423] and other medical conditions [356] compared with HIV-negative women.

3.5.2 Effect of maternal ART on perinatal outcomes

To assess the effect of antenatal ART on perinatal outcomes further, meta-analyses comparing the risk of adverse perinatal outcomes in HIV-positive women on ART versus those not on ART during pregnancy were performed in the present study. The meta-analyses of unadjusted effect estimates revealed that the use of ART during pregnancy was associated with a reduced risk of PTB, LBW and VLBW compared with no ART. Overall, the associations were strongest and most consistent in retrospective cohorts and in studies conducted in high-income countries, and among women receiving non HAART and non PI-based regimens. The secondary outcome of MTCT was significantly less likely in HIV-positive

women receiving ART than those not receiving ART; this finding was consistent across cohort design, and irrespective of ART complexity and class. In the meta-analyses of adjusted effect estimates, antenatal ART remained associated with a reduced risk of PTB, but not other adverse perinatal outcomes.

The above findings suggest that control of HIV progression using ART during pregnancy reduces the risk of adverse perinatal outcomes, especially PTB. Improved maternal health and prevention of *in utero* HIV infection may partly explain why babies born to treated HIV-positive women had a lower risk of adverse perinatal outcomes than those born to untreated HIV-positive women [355]. However, the present findings are different to those in the previous review [62], which showed no association between antenatal ART and PTB compared with no treatment. This previous review [62] only analysed PTB and included 6 English-language studies published up to 2006. Furthermore, sub-group analyses by cohort design and country-income status, sensitivity analyses and meta-analyses of adjusted effect estimates were not performed [62]. By contrast, the present systematic review analysed more adverse perinatal outcomes (not only PTB); included up-to-date studies in any language (published in 1980–2018), and performed robust sub-group and sensitivity analyses and meta-analyses of adjusted effect estimates.

A potentially important source of bias in the present analysis is that the included studies were conducted over a long period, 1984 to 2017 (Table 3.3). During that time, ART guidelines changed: from when ART was not widely available (before 1994) [112] to option A and option B in 2010 [58], option B+ in 2013 [59], and

"treat all" recommendations in 2015 [12]. Different ARVs used at various time points and in different settings could have differential impacts on the risk of adverse perinatal outcomes. Furthermore, in the meta-analysis assessing the risk of adverse perinatal outcomes in untreated HIV-positive versus treated HIV-positive women, most untreated women were recruited before ART became widely available, whereas the treated women were recruited after that. Changes in obstetric care could also have contributed to the observed differences in perinatal outcomes between the two study periods. For example, if antenatal care aimed at preventing adverse perinatal outcomes in the ART era had been more advanced than before-ART era, this would have attenuated the association between antenatal ART and adverse perinatal outcomes.

3.5.3 Effect of ART complexity on perinatal outcomes

The meta-analyses of unadjusted effect estimates showed that dual therapy was not associated with any adverse perinatal outcomes compared with monotherapy. However, HAART was associated with an increased risk of PTB, LBW and SGA compared with monotherapy. These associations were most consistent in prospective cohorts and in studies conducted in LMICs, and the magnitude of these associations was highest in PI-based HAART. Compared with dual therapy, HAART remained associated with an increased risk of PTB. Both dual therapy and HAART were associated with a reduced risk of MTCT compared with monotherapy, and the evidence was strongest in HAART. In the meta-analyses of adjusted effect estimates, dual therapy remained not associated with PTB; however, HAART remained associated with an increased risk of PTB, LBW and SGA compared with monotherapy.

To my knowledge, this is the first systematic review and meta-analysis that has specifically assessed the risk of adverse perinatal outcomes according to three different ART complexities: monotherapy, dual therapy and HAART. The present finding of an increased risk of adverse perinatal outcomes in women on HAART compared with those on monotherapy is consistent with a network meta-analysis of RCTs [216]. However, the network meta-analysis was unable to compare the risk of adverse perinatal outcomes in women on dual therapy versus monotherapy, or HAART versus dual therapy [216]. Furthermore, a previous pairwise meta-analysis with only seven English-language studies published up to 2006, showed no difference in PTB risk between women receiving combination therapy versus women receiving monotherapy [62]. However, this previous meta-analysis did not differentiate women who received HAART from those who received dual therapy [62].

HAART has reassuringly shown the strongest effect on reducing the risk of vertical HIV transmission compared with dual therapy and monotherapy. However, in the context of perinatal outcomes, the use of a combination of at least three ARVs may increase toxic effects and the possibility of drug-drug interactions, especially in LMICs where women frequently have lower BMI [433] and a higher prevalence of acute co-infections that need additional medications [434-436].

A potential source of bias in the present analysis is that HAART has been recommended for women with more advanced immunosuppression (CD4 ≤350 cells/μL), whereas ZDV monotherapy has been for women with less advanced

immunosuppression (CD4 >350 cells/μL) [58]. This was observed in several studies [14,16,28,356,396,403,429] included in the present systematic review; even in other included studies, HAART was indicated for women with CD4 ≤250 cells/μL [15] or CD4 <200 cells/μL [17,24,397].

3.5.4 Effect of ART class on perinatal outcomes

The meta-analyses of unadjusted effect estimates revealed an association between PI-based regimens and an increased risk of PTB compared with non PI-based regimens, and this finding was consistent in prospective cohorts. PI-based regimens were also associated with an increased risk of VPTB; however, this association was observed in studies conducted in LMICs only. In retrospective cohorts, PI-based regimens were associated with a reduced risk of LBW; however, in prospective cohorts, PI-based regimens were associated with an increased risk of LBW compared with non PI-based regimens. In sensitivity analyses limited to women on HAART, PI remained associated with an increased risk of PTB, although at borderline statistical significance. The meta-analyses of adjusted effect estimates showed a borderline significant association between PI-based regimens and an increased risk of PTB; this association became significant in the sub-group analysis of retrospective, but not prospective cohorts. Overall, these findings persisted in the sensitivity analyses restricted to women on HAART.

For the meta-analysis of unadjusted effect estimates, the present findings are consistent with a meta-analysis published in 2007 [62], which also showed a higher risk of PTB in women on PI-based ART than in those on non PI-based

ART. However, it only included eight English-language studies published up to 2006; of these, three were included in the present meta-analysis [23,382,383]. The findings are also consistent with a network meta-analysis of RCTs [216] regarding the effect of PI-based ART on PTB risk. However, for the effect of PI-based ART on LBW, the present findings are different from that network meta-analysis [216], which showed a higher risk of LBW in women receiving PI-based ART than in those receiving non PI-based ART.

The present meta-analysis of adjusted effect estimates only showed a borderline significant association between PI-based ART and PTB risk, unlike a meta-analysis published in 2016 [63] that showed a significant association between PI-based ART and PTB risk. Nevertheless, it only included 10 English-language studies published up to 2013 [63]; of these, three [380-382] were also included in the present meta-analysis. Furthermore, only PTB was analysed; duration of antenatal ART exposure was not defined; systematic and robust literature searching, and sub-group analyses by study design and country-income status were not performed [63]. In addition, an ambiguous comparator was used [63]. For example, in one of the included studies [383], untreated HIV-positive was used as a comparator; however, in other included studies [371,372], unspecified monotherapy and dual therapy were used as a comparator. Among the 10 studies included in this previous meta-analysis [63], three different definitions of PTB were used: <36, <37 and ≤37 weeks' gestation. Moreover, it included two studies [372,380] that probably overlapped because women from the same study population – the International Maternal Pediatric and Adolescent AIDS Clinical Trials (Protocol P1025) – were recruited.

The proposed mechanisms through which PI-based ART increases PTB risk include an increased placental expression of the progesterone metabolizing enzyme 20-α-hydroxysteroid dehydrogenase that may lead to decreased progesterone levels [437], and an effect of ritonavir-boosted PIs on preventing glucocorticoid metabolism, which in turn leads to higher prostaglandin levels via the maternal-fetal hypothalamic pituitary axis [20]. In addition, a previous study [372] has shown an effect of PI specific drugs – saquinavir, ritonavir and lopinavir/ritonavir – on increasing PTB risk.

A potential source of bias is that, in several studies included in the present systematic review [18,366,407,421,428], women receiving PI-based ART had more advanced HIV disease than those receiving non PI-based ART, which would have augmented the association between PI-based ART and PTB [365]. Another important source of bias is that PIs have been frequently prescribed as HAART and even with ritonativir, as an additional booster agent. On the other hand, non PIs have been prescribed as monotherapy, dual therapy and HAART without any booster agent [15,18,21,22,24,30,96,154,369,382,383,407]. Therefore, women receiving PI-based ART could have more toxic effects and drug-drug interactions compared with those receiving non PI-based ART. This may explain why the significant association of PI-based ART with an increased risk of PTB in the meta-analysis of unadjusted effect estimates became borderline significant when the analysis was restricted to those receiving PI and non PI-based HAART.

3.5.5 Effect of timing of ART initiation on perinatal outcomes

The pooled unadjusted effect estimates showed a higher risk of PTB and VPTB in women starting ART pre-conception than those starting post-conception. For PTB, this finding was consistent in the sub-group analyses of retrospective cohorts, and studies conducted in LMICs. Pre-conception initiation was also associated with a higher risk of SGA; however this was observed in the sub-group analysis of retrospective cohorts only. For women in LMICs, initiating ART before pregnancy was associated with an increased risk of VSGA; however, for women in high-income countries, initiating ART before pregnancy was associated with a reduced risk of VSGA. In addition, women starting ART pre-conception showed a lower risk of vertical HIV transmission than those starting ART post-conception. In sensitivity analyses limited to women on HAART, pre-conception initiation remained associated with an increased risk of PTB, particularly in LMICs. This association was observed in women receiving both non PI and PI-based HAART; however for PI-based HAART, the association was borderline significant. The pooled adjusted effect estimates showed that pre-conception initiation of ART remained associated with an increased risk of PTB, which remained even when the analysis was limited to women on HAART. This evidence was strongest and most consistent in LMICs. Furthermore, the pooled adjusted effect estimates showed a higher risk of SGA in women initiating HAART prior to conception than in those initiating after conception.

Among women starting ART after conception, first trimester initiation (versus after first trimester) was consistently not associated with any adverse perinatal

outcomes in the meta-analysis of unadjusted and adjusted effect estimates, sub-group analyses and sensitivity analyses.

The present finding that PTB was significantly more common when ART was initiated before conception is consistent with a previous systematic review of studies published up to 2016 [64], which was based on only unadjusted effect estimates of 11 cohorts, involving women all on HAART [64]. Of these 11 cohorts, five [15,18,24,376,403] were also pooled in the present systematic review. Two different definitions of VPTB (<34 and <32 weeks' gestation) were used in the studies included in the previous review [64], which may have resulted in misclassification bias. Furthermore, the duration of antenatal ART exposure was not defined in the previous review [64]: some women, therefore, may have received antenatal ART for <30 days.

The association between pre-conception initiation of ART and PTB is elusive, yet intriguing. Although PTB is a complex, highly heterogeneous syndrome with multiple aetiologies, the most frequent clinical phenotype is inflammation [228]. Women initiating ART before conception should have higher median CD4 counts, suppressed viral load and a lower risk of opportunistic infections. Therefore, it seems biologically implausible that starting ART before conception increases the risk of PTB. The finding of the present meta-analysis, and the previous one [64], should be interpreted in the context of study methodologies. All studies included in the present meta-analysis were observational with inherent characteristics prone to biases. One example is selection bias, as women who had delivered preterm infants before commencing ART were systematically excluded from the analyses

[438], which would have reduced the risk of PTB among the remaining women. Given that this exclusion is only relevant for women starting ART post-conception, the magnitude of effect size for PTB risk in women starting ART pre-conception compared with those starting post-conception is inevitably inflated. Moreover, most studies included in the present meta-analysis did not report the median gestational age when ART was initiated, thus hindering the assessment of potential selection bias.

Another potential source of bias is that women starting ART prior to conception could have more risk factors for PTB than those starting ART after conception. As observed in several studies included in the present meta-analysis, women starting ART prior to conception were older [13-15,24,29,356,403,417] less educated [14,15,403], and more likely to have lower nadir CD4 counts [24,417] and a history of adverse perinatal outcomes [15,29] and other medical conditions [24,403] compared with women starting ART after conception. Although the present meta-analysis of adjusted effect estimates has controlled for these risk factors, residual unmeasured confounding could still remain. However, it is still possible that pre-conception initiation of ART increases the risk of PTB through an indirect effect on pregnancy complications [439] that lead to medically indicated PTB.

To my knowledge, this is the first meta-analysis assessing the risk of adverse perinatal outcomes in women initiating ART in the first trimester compared to those initiating ART after the first trimester. This analysis is important for women diagnosed with HIV-positive after conception. However, the present finding of no

association between first trimester initiation and adverse perinatal outcomes should be interpreted cautiously due to the high risk of selection bias, as mentioned above.

3.5.6 Different findings by country-income status

Overall, the above findings have shown that the effects of maternal HIV/ART, antenatal ART, different ART complexity and class, and different timing of ART initiation on adverse perinatal outcomes in LMICs are not the same as in high-income countries. The first reason for this is different ART regimens used in each setting. While WHO-recommended first-line TDF+FTC/3TC+EFV has been widely used in LMICs since 2012 [12,59,377], this regimen has been downgraded as an alternative regimen in the US and several European countries due to EFV-related toxic effects [355]. In fact, in the US, PI-based ART has been designated as the preferred regimen in pregnancy [440]. Second, women in LMICs frequently have lower BMIs [433], which might result in higher drug concentrations and, in turn, increased ARV toxicity. Third, due to a higher incidence of acute co-infections [434-436], additional medications may be needed by women in LMICs, increasing the possibility of drug-drug interactions with ART. Fourth, ARV toxicity may have a more marked impact in LMICs due to limited resources for clinical and laboratory monitoring. Lastly, LMICs, particularly in sub-Saharan Africa, have the highest burden of maternal HIV infection [60], and high rates of fertility [441] and adverse perinatal outcomes [6,7,256]; as a result, there may have been increased statistical power to observe differences in adverse perinatal outcomes, especially for rare outcomes (VPTB, VSGA).

3.5.7 Strengths and limitations

The present study has several strengths. To my knowledge, this is the first systematic review and meta-analysis summarising the effects of maternal HIV/ART, antenatal ART, ART complexity and class, and timing of ART initiation on perinatal outcomes in a single account. Second, the present meta-analysis was based on a pre-defined protocol so as to minimise any bias in the conduct of the review. Third, all steps of the review process were conducted by two independent investigators. Fourth, the literature search was comprehensive, rigorous and updated (publications in 1980–2018), with no language or geographical restrictions. Fifth, the inclusion of observational studies has provided the best possible evidence to compare the risk of adverse perinatal outcomes in treated HIV-positive versus untreated HIV-positive women, and to compare the risk of adverse perinatal outcomes according to timing of ART initiation (pre-conception versus post-conception, first-trimester versus after first-trimester initiation). Sixth, unlike the previous meta-analyses, which only included PTB [62,63], the present meta-analysis included PTB and other perinatal outcomes: VPTB, LBW, VLBW, SGA, VSGA, stillbirth, NND and MTCT. Seventh, stringent eligibility criteria, including adverse perinatal outcomes of interest and the minimum duration of ART exposure during pregnancy were clearly defined *a priori* so as to reduce the risk of misclassification bias and to ensure that there was a reasonable duration for antenatal ART to affect perinatal outcomes. Eighth, whilst the previous meta-analyses only summarised unadjusted [62,64] or adjusted effect estimates [63], the present meta-analysis summarised both effect estimates controlling for confounding factors relevant for individual

studies. Ninth, in order to explore unexplained heterogeneity, several sub-group analyses were performed, and several sensitivity analyses were performed to determine the robustness of the observed summary effect estimates. Finally, the systematic review was reported according to the PRISMA guidelines [393].

However, the present study also has several limitations. First, as mentioned above, all studies included in the present systematic review and meta-analysis were observational and therefore prone to biases. Although a meta-analysis of adjusted effect estimates was performed in the present study, residual unmeasured confounding could still exist. Second, because not all studies reported adjusted ORs, only those reporting adjusted ORs were included in the meta-analysis of adjusted effect estimates. For example, in the meta-analysis assessing the risk of PTB in HIV-positive women on ART versus those not on ART, 17 studies were included in the meta-analysis of unadjusted effect estimates (Figure 3.12). Of these 17 studies, only five reported adjusted ORs and were included in the meta-analysis of adjusted effect estimates (Figure 3.14). Had the other 12 studies also provided adjusted ORs and been included in the meta-analysis of adjusted effect estimates in Figure 3.14, the observed summary effect size might have been different. Third, several studies reported multiple adjusted ORs for different ART exposures compared with the same comparator. For instance, in the study by Moodley et al. [28], three adjusted ORs were reported for the risk of PTB in HIV-positive women receiving ZDV monotherapy (adjusted OR: 0.20), EFV-based HAART (adjusted OR: 0.31) and NVP-based HAART (adjusted OR: 0.21) compared with the same comparator: HIV-positive without treatment (Figure 3.15). Women with these three different ART exposures basically could be

combined into one group of treated HIV-positive women. Although pooling these three adjusted ORs in a single forest plot of treated HIV-positive versus untreated HIV-positive women in Figure 3.14 might have increased the statistical power, this approach should be avoided because untreated HIV-positive women (comparator) would be counted three times [384]. Fourth, the adjusted ORs controlled for various covariates relevant to individual studies, and these covariates could be different among the included studies. For example, Chen et al. [15] controlled for education, marital status, smoking, alcohol consumption, history of adverse perinatal outcomes, gestational hypertension, anemia, history of TB and CD4 cell count; however, Zash et al. [96,404,405] controlled for age, education and gravidity (Table 3.5). Fifth, studies reporting severe adverse perinatal outcomes (VPTB, VLBW and VSGA) and fetal/neonatal mortality were lacking, thereby preventing the overall meta-analysis, sub-group and/or sensitivity analysis. Therefore, a firm conclusion cannot be drawn for these outcomes. The inclusion of studies in which severe adverse perinatal outcomes were not defined or defined differently to the study protocol, as occurred in the previous meta-analyses [63,64], might have increased the power of the present analyses; however, this would have introduced bias. Severe adverse perinatal outcomes would be interesting to examine because they are associated with greater infant morbidity and mortality compared with moderate adverse perinatal outcomes (PTB, LBW and SGA). Sixth, studies reporting adverse perinatal outcomes according to four different classes of ART – NRTI, NNRTI, INSTI and PI – were very limited, preventing the meta-analysis by these classes. Therefore, the present meta-analysis only compared the risk of adverse perinatal outcomes in women on

PI versus non PI-based ART (a composite of NRTI, NNRTI and INSTI). Seventh, in most of the included studies, no distinction was made between spontaneous and medically indicated PTB. Eighth, studies reporting MTCT only (without adverse perinatal outcomes) were excluded from the present meta-analysis; the findings on MTCT could be different if the excluded studies were added to the meta-analyses assessing the risk of MTCT. Ninth, information on methods used to estimate gestational age was provided in nearly two-thirds of the included studies, but most did not use first trimester ultrasound scanning – the most accurate method to estimate gestational age [79]. This limitation might have resulted in misclassification of adverse perinatal outcomes and some of the heterogeneity observed. Tenth, SGA and VSGA infants were classified using various reference charts used at the study sites rather than international standards [422]. Eleventh, in the meta-analysis of observational studies, the I^2 values were typically high and potentially exaggerated, so these values should be interpreted cautiously. Lastly, of the total 79 cohorts summarised in the present review, 49 (62%) were retrospective which may have introduced a higher risk of bias than if the cohorts had been prospective – a concern that was addressed by performing a sub-group analysis by cohort design.

3.5.8 Implications of findings

The benefits of antenatal ART for improving maternal health and reducing vertical HIV transmission have reassuringly outweighed any potential risks identified so far. Given RCTs assessing the safety of ART in pregnancy have been lacking, ongoing ART safety surveillance is critical and should be a global public health priority. This surveillance enables the refinement of optimal ART regimens

to allow healthy pregnancies with minimal risk of adverse perinatal outcomes in HIV-positive women. The present systematic review and meta-analysis provides several directions for future studies and practice, as an attempt to strengthen current surveillance efforts.

3.5.8.1 Implications for future studies

First, in view of the fact that current ART safety surveillance programmes for pregnant women are mainly based on observational studies, the present systematic review emphasises the importance of reporting adjusted effect sizes controlling for relevant confounding factors. Therefore, the risk of obtaining biased summary effect sizes could be minimised. Second, future studies need to investigate risk factors for adverse perinatal outcomes in treated HIV-positive and HIV-negative women separately in order to determine whether these risk factors are more common in one group. Third, mechanistic studies investigating underlying pathways or causal mechanisms that threaten perinatal outcomes in HIV-positive women on ART are urgently needed, so as to determine whether these pathways or mechanisms are manageable or modifiable in order to reduce or prevent adverse perinatal outcomes. Fourth, studies assessing differences in adverse perinatal outcomes among four ART classes – NRTI, NNRTI, INSTI and PI – need to be conducted; this is even more critical in view of WHO considerations for ART transition from EFV NNRTI-based to dolutegravir (DTG) INSTI-based ART for all HIV patients, including pregnant women [222]. Fifth, in the absence of RCTs investigating the association between timing of ART initiation and adverse perinatal outcomes, it is crucial that future studies provide the distribution of gestational age at ART initiation so as to enable the assessment of potential

selection bias. Sixth, the present review has shown that the majority of included studies did not distinguish sPTB from medically indicated PTB; there is, therefore, a need to distinguish these two adverse perinatal outcomes. Spontaneous PTB has been associated with maternal HIV infection, whereas medically indicated PTB has been associated with the use of HAART [411]. Seventh, in order to minimise the risk of misclassification of adverse perinatal outcomes, future studies should use the most accurate method to estimate gestational age, i.e. a first trimester ultrasound [79]. Eighth, given that various reference charts have been used to classify SGA and VSGA newborns, the present review highlights the need for using international standards, e.g. the INTERGROWTH-21st Newborn Size Standards [442] – thus enabling international comparison and reducing the risk of misclassification bias. Ninth, the scarcity of severe adverse perinatal outcomes (VPTB, VLBW, VSGA, stillbirth, NND) has opened opportunities to conduct pooled analyses or meta-analyses across surveillance cohorts. Tenth, on the grounds that previous meta-analyses used ambiguous definitions of adverse perinatal outcomes and comparators [62-64], any attempt to conduct meta-analyses must ensure that the definitions of adverse perinatal outcomes and comparators are similar in all individual studies.

3.5.8.2 Implications for practice

First, the present meta-analysis has shown a reduced risk of adverse perinatal outcomes in HIV-positive pregnant women on ART compared with those not on ART; therefore, there is no doubt that lifelong ART should be initiated in all HIV-positive women. Second, due to a high risk of selection bias in the present finding of an increased risk of PTB in women starting ART pre-conception compared

with those starting post-conception, clinicians should not withhold ART from all HIV-positive women just to avoid PTB. Third, with the present findings of an increased risk of adverse perinatal outcomes in women receiving HAART and PI-based regimens and the current recommendations for immediate initiation of lifelong HAART [12] for the 1.4 million pregnancies every year in HIV-positive women [443], there is a need to establish international programmatic prospective birth registries focusing on the collection of perinatal outcomes in HIV-positive women. The measurement of perinatal outcomes in all birth registries should be conducted in a standardised manner: 1) the use of a first-trimester ultrasound to estimate gestational age, 2) standardised techniques and instruments to measure birth weight within 24h of birth, 3) the use of the INTERGROWTH-21st Newborn Size Standards to classify SGA and VSGA newborns. In order to facilitate the pooled collaborations, linkages could be created between birth registries. This programme surely calls for advanced planning, strenuous efforts and cooperation between stakeholders.

Chapter 4: Overlap between measures of perinatal outcomes based on accurately determined gestational age and birth weight.

4.1 Introduction

Numerous epidemiological and clinical studies have explored an array of related and overlapping measures of perinatal outcomes (such as gestational age and birth weight), or a derivative of these two measures (birth weight for gestational age). For example, low birth weight (LBW) comprises a mixture of babies who are constitutionally small, and small because of being born preterm (<37 weeks' gestation) and/or growth restricted (intrauterine growth restriction, IUGR) [251,252]. Existing evidence has shown that babies born preterm or small for gestational age (SGA) [238,240,257,444-449] or LBW [450-453] have an increased risk of neonatal morbidity and mortality. In addition, these three perinatal outcomes – preterm birth (PTB), LBW and SGA – have been used as a surrogate indicator of a population's infant risk for morbidity and mortality, although LBW is the most commonly used [251,252,454]. Therefore, the identification of preventable or modifiable risk factors for these perinatal outcomes, as an attempt to reduce infant morbidity and mortality, has been a popular topic in epidemiological studies.

For risk factor identification, perinatal outcomes should be classified as uniformly as possible. If two perinatal outcomes define the "same" babies, there is clearly an overlap between them – suggesting that they are equivalent and should not be treated as discrete outcomes. For instance, if the vast majority of LBW babies are born preterm and vice versa, it might not be worthwhile to analyse PTB and LBW separately. Conversely, if two perinatal outcomes define "different" babies, there is no overlap – suggesting that they are functionally distinct and worth differentiating in analyses. For instance, if the vast majority of PTB babies are not SGA and vice versa, it might be an indication that these two perinatal outcomes have different risk factors and mechanistic pathways.

For the overlap analysis, perinatal outcomes should be measured using the most accurate methods so as to prevent any measurement error and misclassification. Gestational age should ideally be estimated using first trimester ultrasound [79], birth weight should be directly measured in a standardised manner within 24h of birth [455], and birth weight for gestational age should ideally be classified using international standards, e.g. the INTERGROWTH-21st Newborn Size Standards [442], not local reference charts. However, in the previous overlap analysis [454], gestational age was estimated using less accurate parameters, e.g. last normal menstrual period (LNMP), late ultrasound (or the two combined), and clinical assessment; birth weight was not measured in a standardised manner within 24h of birth, and birth weight for gestational age was classified using different local reference charts.

This chapter assesses the overlap between measures of perinatal outcome based on prospectively and accurately collected data in South Africa – a country with the highest number of HIV-positive people in the world [1], where one in three pregnant women are HIV-positive [350]. All women were recruited and dated using an ultrasound <14 weeks' gestation, and followed up until delivery at which time the perinatal outcomes of interest were measured.

4.2 Aims

This chapter aims to assess:

1. The overlap between measures of perinatal outcome based on accurately determined gestational age and birth weight among South African newborns, irrespective of *in utero* HIV-exposure status.
2. The overlap between measures of perinatal outcome in HIV-unexposed versus HIV-exposed South African newborns.

4.3 Methods

4.3.1 Study setting

The study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa; the only public referral hospital in Soweto. This is the largest referral hospital in Africa (>3,000 beds) with approximately 20,000 births per year; of these, 30% occur in HIV-positive women [456,457]. Around 60 community health centres also provide pregnancy care in Soweto; however, CHBAH is the only public hospital with ultrasound facilities [457].

4.3.2 Study design

INTERBIO-21st is a longitudinal cohort study conducted at seven study sites in six countries: Oxford, UK; Pelotas, Brazil; Mae Sot, Thailand; Karachi, Pakistan; Kilifi, Kenya; Nairobi, Kenya; and Soweto, South Africa. The study aimed to produce a more functional phenotypic characterisation of the IUGR/SGA and PTB syndromes, based on the accurate assessment of birth weight and gestational age, as well as a range of clinical factors and outcomes, including growth morbidity and neurodevelopment up to two years of age. The ultimate aim is to produce more effective and targeted strategies to improve pregnancy and newborn outcomes [458]. Only data collected at Soweto study site were analysed here.

4.3.3 Participants

Women needed to meet the following inclusion criteria: living in Soweto, aged ≥18 years, with a singleton, spontaneously conceived pregnancy, and gestational age <14 weeks at first visit. Women with multiple pregnancies, BMI >35 kg/m^2 (as obesity affects the accuracy of ultrasound scans), or intellectual/physical disability were excluded. Women who met the inclusion criteria were enrolled and followed until delivery (see 4.3.4 Data collection). Only live newborns with information on both gestational age at delivery and birth weight were included in the present overlap analysis.

4.3.4 Data collection

Data collection was conducted at study enrolment, during follow-up visits and at delivery (Figure 4.1). Women were enrolled from May 28, 2013 to December 24, 2015. At enrolment, comprehensive and detailed information on baseline maternal

characteristics was collected from face-to-face interviews, direct measurements and medical records. This information included a total of around 200 items encompassing socio-demographic and nutritional characteristics; medical, obstetric and gynaecological history, and other conditions related to the pregnancy. A dating ultrasound scan was performed at 9^{+0} to 13^{+6} weeks' gestation in all women. At each follow-up visit (every 5±1 weeks) until delivery, an ultrasound scan was performed to monitor fetal growth and any changes in maternal health status since the previous visit were documented. At the time of birth (from September 21, 2013 to July 20, 2016), the perinatal outcomes of interest were measured (Figure 4.1).

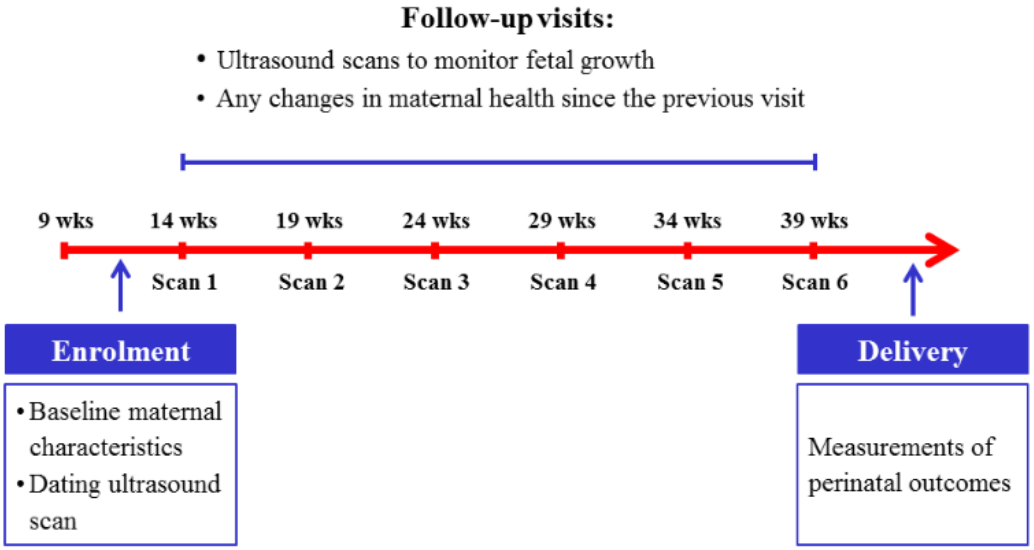


Figure 4.1. Data collection periods in the INTERBIO-21st Study. Abbreviation: wks, weeks.

4.3.5 *In utero* HIV-exposure status

Newborns were classified as *in utero* HIV-exposed if the routine maternal HIV test conducted either before or during pregnancy was positive, and HIV-unexposed if the maternal HIV test was negative.

4.3.6 Measures of perinatal outcomes

4.3.6.1 Definitions

Gestational age was classified into two categories: PTB and term, defined as a live birth <37 and ≥37 weeks' gestation, respectively. Birth weight was classified into two categories: LBW and normal birth weight (NBW), defined as a live birth <2500 and ≥2500g, respectively. Birth weight for gestational age was classified into two categories: SGA and not SGA, defined as a live birth <10th and ≥10th centile of the INTERGROWTH-21st Newborn Size Standards, respectively [442].

4.3.6.2 Measurements

4.3.6.2.1 Gestational age

At enrolment, a transabdominal ultrasound scan was performed by a trained and dedicated ultrasonographer to measure the fetal crown-rump length (CRL) using a commercially available ultrasound machine, Philips™ HD-9 (Philips, Massachusetts, USA). Only women with a confirmed gestational age <14 weeks remained in the study.

4.3.6.2.2 Birth weight

Birth weight was measured within 12h of birth (and no later than 24h) using a Seca™ 376 baby scale (Seca, Germany) and performed independently by two trained anthropometrists. If the two anthropometrists recorded different results and the difference was more >50g, the measurement was repeated by each anthropometrist. If the difference was still >50g, a third repetition was carried out; after the third measurement, if the difference was still >50g, all results were reported on the form and the average was used for this analysis. The equipment,

which was calibrated twice weekly, was selected for accuracy, precision and robustness, as demonstrated in previous studies [459].

4.3.7 Statistical analysis

Each perinatal outcome was paired with another: thus, three perinatal outcome pairs were analysed: 1) gestational age and birth weight, 2) gestational age and birth weight for gestational age, and 3) birth weight and birth weight for gestational age. The overlap between selected pairs was assessed by generating 2x2 contingency tables. The proportion of newborns in one perinatal outcome category that also met the criteria for another was presented, e.g. the proportion of PTB newborns that were also LBW and vice-versa. Cohen's kappa (κ) coefficient and 95% confidence intervals (CIs) were estimated to examine the overlap between two perinatal outcomes after taking into account the overlap that would be expected purely by chance. Kappa coefficient <0.00 indicates "poor", 0.00 to 0.20 "slight", 0.21 to 0.40 "fair", 0.41 to 0.60 "moderate", 0.61 to 0.80 "substantial", and 0.81 to 1.00 "almost perfect" agreement [460]. Statistical analyses were performed using STATA™ version 15.1 (StataCorp, Texas, USA).

4.3.8 Ethical considerations

Prior to study enrolment, women were provided with a patient information leaflet, detailed study description and informed consent form. Only those who consented to participate in the study were enrolled. The study was approved by the University of Oxford Tropical Research Ethics Committee (OxTREC) and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa.

4.4 Results

From the 680 women enrolled in the INTERBIO-21st Study, 47 were excluded because of loss to follow-up (n=36) or withdrawal of consent (n=11). Among 633 women followed until delivery, 37 were excluded due to miscarriage. From the remaining 596 deliveries, 26 newborns were excluded (stillbirths = 18; live newborns without information on birth weight = 8). A total of 570 live newborns with information on both gestational age and birth weight were included in the overlap analysis (HIV-unexposed = 360; HIV-exposed = 210, Figure 4.2). Information on the birth weight for gestational age/sex centile was not available in two newborns (one HIV-unexposed and one HIV-exposed) because of being born outside the 24-42 weeks' gestational age range [461]. Therefore, the overlap analysis of birth weight for gestational age included a total of 568 newborns (HIV-unexposed = 359; HIV-exposed = 209). Table 4.1 presents the number and proportion of newborns according to gestational age, birth weight and birth weight for gestational age/sex in all newborns, HIV-unexposed and HIV-exposed newborns.

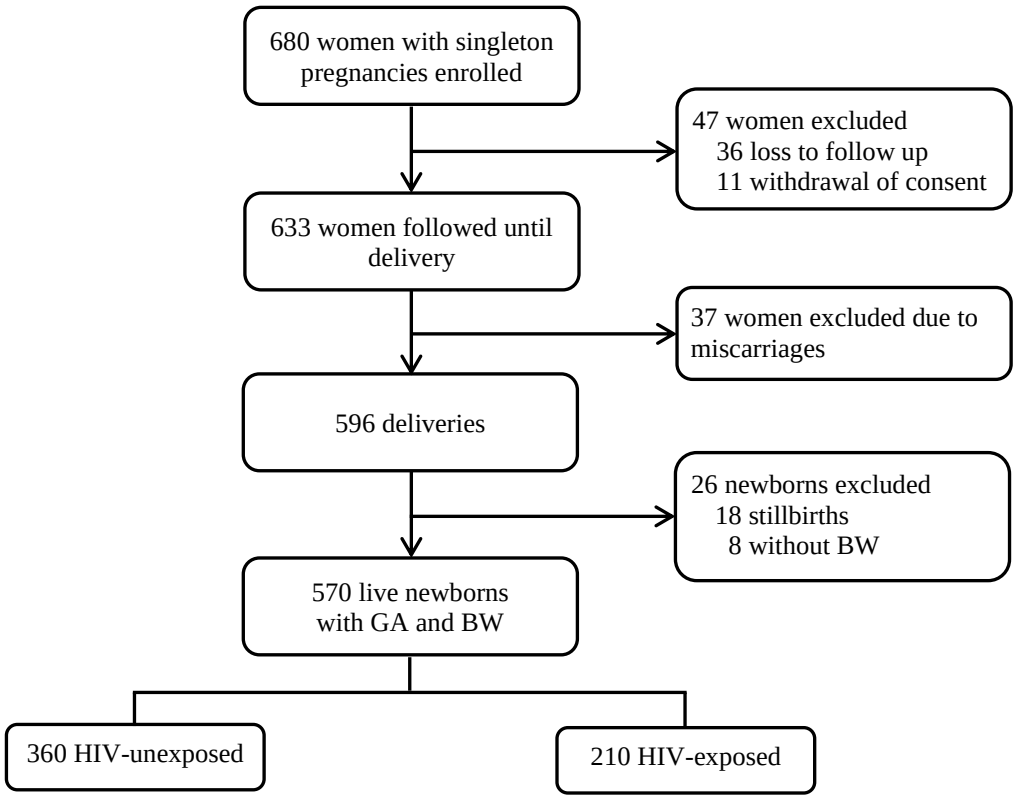


Figure 4.2. Flow diagram of study participants. Abbreviations: BW, birth weight; GA, gestational age; HIV, human immunodeficiency virus.

Table 4.1. Number and proportion of newborns according to gestational age, birth weight, birth weight for gestational age/sex and *in utero* HIV-exposure status.

Measures of perinatal outcomes	**All newborns (N=570) n (%)**	**HIV-unexposed (N=360) n (%)**	**HIV-exposed (N=210) n (%)**
Gestational age (weeks)			
<37	94 (16.5)	55 (15.3)	39 (18.6)
≥37	476 (83.5)	305 (84.7)	171 (81.4)
Birth weight (g)			
<2500	114 (20)	67 (18.6)	47 (22.4)
≥2500	456 (80)	293 (81.4)	163 (77.6)
Birth weight for gestational age/sex (centile)[§]			
<10th	106 (18.7)	58 (16.2)	48 (23)
≥10th	462 (81.3)	301 (83.8)	161 (77)

[§] Two deliveries were outside the range of 24-42 weeks' gestation.
Abbreviation: HIV, human immunodeficiency virus.

4.4.1 Overlap between gestational age and birth weight

4.4.1.1 Analysis in all newborns

The overlap between gestational age and birth weight in all newborns is presented in Table 4.2. Blue downward arrows (Table 4.2) refer to the proportion of newborns who had an outcome indicated in the column and also had another outcome indicated in the intersecting row. For example, among preterm newborns, 80.9% and 19.1% were LBW and NBW, respectively (Table 4.2). Blue rightward arrows (Table 4.2) refer to the proportion of newborns who had an outcome indicated in the row and also had another outcome indicated in the intersecting column. For example, among LBW newborns, 66.7% and 33.3% were preterm and term, respectively (Table 4.2). For term and NBW, the overlap was high: 92% of term newborns were NBW, 96.1% of NBW newborns were term (Table 4.2). PTB was predictive of being classified as LBW: 80.9% of preterm versus 8% of term newborns were LBW. Similarly, LBW was predictive of being PTB: 66.7% of LBW versus 3.9% of NBW newborns were preterm (Table 4.2). Based on the kappa coefficient, the overlap between PTB and LBW was substantial (κ: 0.69, 95% CI: 0.63, 0.75). Figure 4.3 shows a trend of positive linear relationship between gestational age at delivery and birth weight.

Table 4.2. Overlap between gestational age and birth weight in all newborns.

Birth weight	Gestational age	
	↓ <37 weeks (PTB)	↓ ≥37 weeks (Term)
<2500g (LBW) →	80.9% / 66.7%	8.0% / 33.3%
≥2500g (NBW) →	19.1% / 3.9%	92.0% / 96.1%

Abbreviations: LBW, low birth weight; NBW, normal birth weight; PTB, preterm birth.

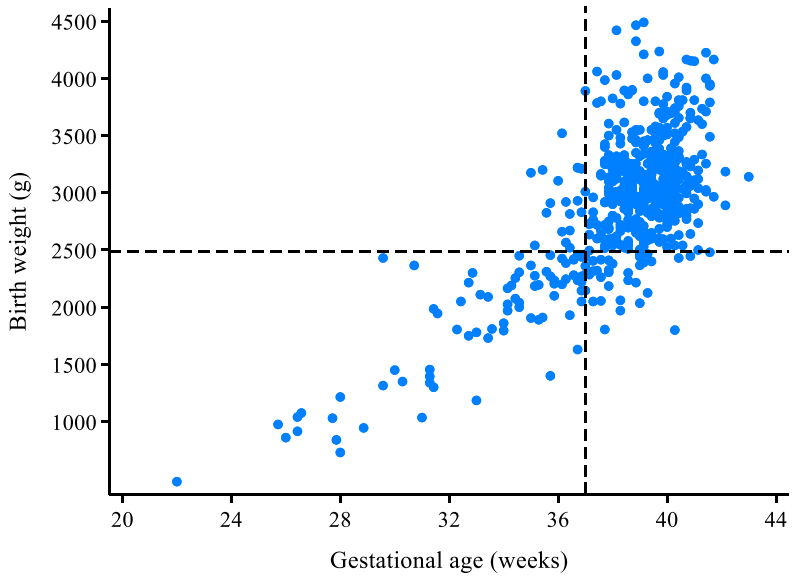


Figure 4.3. Scatter plot of birth weight by gestational age in all newborns. Dashed line, ruled line at cut-off points for defining preterm birth and low birth weight, as appropriate.

4.4.1.2 Analysis by *in utero* HIV-exposure status

Overall, the overlap between gestational age and birth weight in the HIV-unexposed (Table 4.3A) and HIV-exposed groups (Table 4.3B) was similar. In the HIV-unexposed group, 78.2% of preterm newborns were LBW, 64.2% of LBW newborns were preterm, and there was a strong overlap between term and NBW: 92.1% of term newborns were NBW and 95.9% of NBW newborns were term (Table 4.3A). In the HIV-exposed group, 84.6% of preterm newborns were LBW,

70.2% of LBW newborns were preterm, and there was a strong overlap between term and NBW: 91.8% of term newborns were NBW and 96.3% of NBW newborns were term (Table 4.3B). In both groups, PTB was predictive of being classified as LBW. In the HIV-unexposed group, 78.2% of preterm versus 7.9% of term newborns were LBW (Table 4.3A). In the HIV-exposed group, 84.6% of preterm versus 8.2% of term newborns were LBW (Table 4.3B). Similarly, LBW was predictive of being classified as PTB in both groups. In the HIV-unexposed group, 64.2% of LBW versus 4.1% of NBW newborns were preterm (Table 4.3A). In the HIV-exposed group, 70.2% of LBW versus 3.7% of NBW newborns were preterm (Table 4.3B). Kappa coefficients showed a substantial agreement between PTB and LBW in both HIV-unexposed (κ: 0.65, 95% CI: 0.54, 0.75) and HIV-exposed (κ: 0.71, 95% CI: 0.59, 0.83) groups. Figure 4.4 shows a trend of positive linear relationship between gestational age at delivery and birth weight in the HIV-unexposed and HIV-exposed groups.

Table 4.3. Overlap between gestational age and birth weight in HIV-unexposed (A) and HIV-exposed newborns (B).

A.

Birth weight	**Gestational age**	
	↓ <37 weeks (PTB)	**↓ ≥37 weeks (Term)**
<2500g (LBW) →	78.2% / 64.2%	7.9% / 35.8%
≥2500g (NBW) →	21.8% / 4.1%	92.1% / 95.9%

Abbreviations: HIV, human immunodeficiency virus; LBW, low birth weight; NBW, normal birth weight; PTB, preterm birth.

B.

Birth weight	Gestational age	
	↓ <37 weeks (PTB)	↓ ≥37 weeks (Term)
<2500g (LBW) →	84.6% / 70.2%	8.2% / 29.8%
≥2500g (NBW) →	15.4% / 3.7%	91.8% / 96.3%

Abbreviations: HIV, human immunodeficiency virus; LBW, low birth weight; NBW, normal birth weight; PTB, preterm birth.

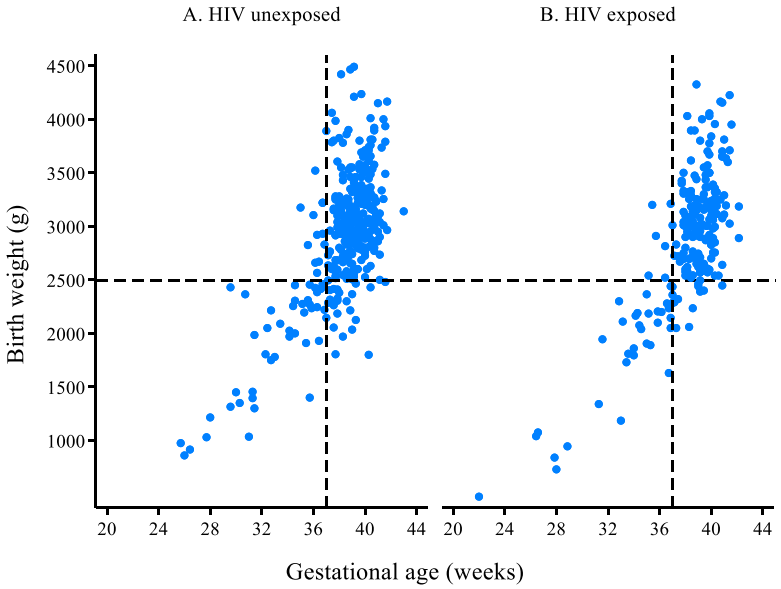


Figure 4.4. Scatter plots of birth weight by gestational age in HIV-unexposed (A) and HIV-exposed newborns (B). Dashed line, ruled line at cut-off points for defining preterm birth and low birth weight, as appropriate.

4.4.2 Overlap between gestational age and birth weight for gestational age/sex

4.4.2.1 Analysis in all newborns

The overlap between gestational age and birth weight for gestational age/sex was very modest. Only 17.2% of preterm newborns were SGA and 15.1% of SGA newborns were preterm (Table 4.4). The overlap between term and not-SGA was quite high: 81.1% of term newborns were not-SGA, 83.3% of not-SGA newborns

were term (Table 4.4). The classification of SGA was independent of PTB: 17.2% of preterm versus 18.9% of term newborns were SGA (Table 4.4). Likewise, the classification of PTB was independent of SGA: 15.1% of SGA versus 16.7% of not-SGA newborns were preterm (Table 4.4). Kappa coefficient indicated that the overlap between PTB and SGA was poor (κ: -0.05, 95% CI: -0.10, -0.01). A scatter plot of birth weight for gestational age/sex by gestational age at delivery is shown in Figure 4.5.

Table 4.4. Overlap between gestational age and birth weight for gestational age/sex in all newborns.

Birth weight for gestational age/sex	Gestational age	
	↓ <37 weeks (PTB)	↓ ≥37 weeks (Term)
<10th centile (SGA) →	17.2% / 15.1%	18.9% / 84.9%
≥10th centile (Not SGA) →	82.8% / 16.7%	81.1% / 83.3%

Abbreviations: PTB, preterm birth; SGA, small for gestational age.

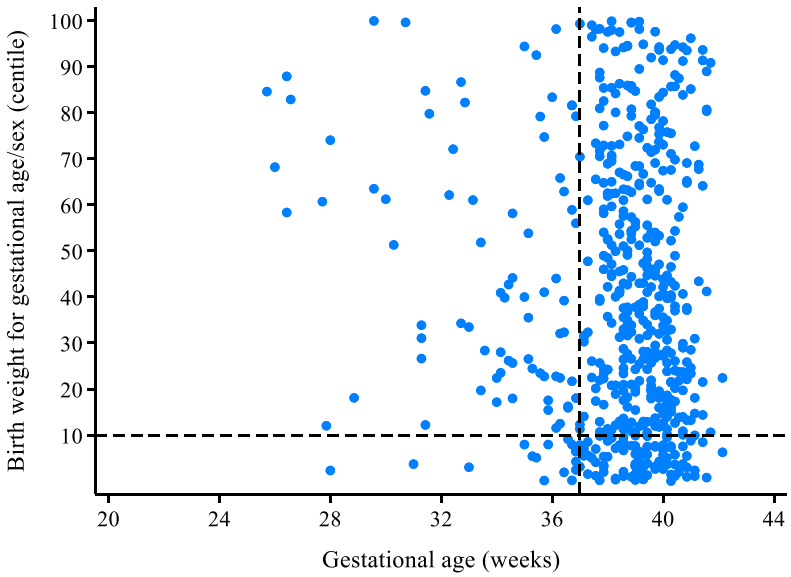


Figure 4.5. Scatter plot of birth weight for gestational age/sex by gestational age in all newborns. Dashed line, ruled line at cut-off points for defining preterm birth and small for gestational age, as appropriate.

4.4.2.2 Analysis by *in utero* HIV-exposure status

The overlap between PTB and SGA was higher in the HIV-exposed than the HIV-unexposed group (Table 4.5): 28.9% of preterm newborns in the HIV-exposed group versus 9.1% in the HIV-unexposed group were SGA; 22.9% of SGA newborns in the HIV-exposed group versus 8.6% in the HIV-unexposed group were preterm (Table 4.5). In both groups, the classification of SGA was independent of PTB and vice versa. In the HIV-unexposed group, 9.1% of preterm versus 17.4% of term newborns were classified as SGA; 8.6% of SGA versus 16.6% of not-SGA newborns were classified as PTB (Table 4.5A). In the HIV-exposed group, 28.9% of preterm versus 21.6% of term newborns were classified as SGA; 22.9% of SGA versus 16.8% of not-SGA newborns were classified as PTB (Table 4.5B). Based on the kappa coefficients, the agreement between PTB and SGA was poor in the HIV-unexposed group (κ: -0.08, 95% CI: -0.17, 0.00); however, the agreement was slight in the HIV-exposed group (κ: 0.07, 95% CI: -0.08, 0.21). Scatter plots of birth weight for gestational age/sex by gestational age in the two groups are presented in Figure 4.6.

Table 4.5. Overlap between gestational age and birth weight for gestational age/sex in HIV-unexposed (A) and HIV-exposed newborns (B).

A.

Birth weight for gestational age/sex	**Gestational age**	
	<37 weeks (PTB) ↓	**≥37 weeks (Term)** ↓
<10th centile (SGA) →	9.1% / 8.6%	17.4% / 91.4%
≥10th centile (Not SGA) →	90.9% / 16.6%	82.6% / 83.4%

Abbreviations: PTB, preterm birth; SGA, small for gestational age.

B.

Birth weight for gestational age/sex	Gestational age	
	↓ <37 weeks (PTB)	↓ ≥37 weeks (Term)
<10th centile (SGA) →	28.9% / 22.9%	21.6% / 77.1%
≥10th centile (Not SGA) →	71.1% / 16.8%	78.4% / 83.2%

Abbreviations: PTB, preterm birth; SGA, small for gestational age.

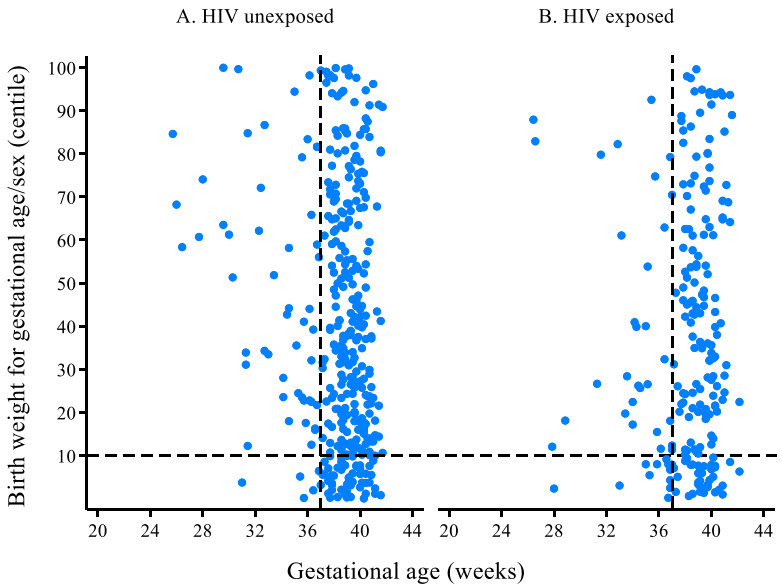


Figure 4.6. Scatter plots of birth weight for gestational age/sex by gestational age in HIV-unexposed (A) and HIV-exposed newborns (B). Dashed line, ruled line at cut-off points for defining preterm birth and small for gestational age, as appropriate.

4.4.3 Overlap between birth weight and birth weight for gestational age/sex

4.4.3.1 Analysis in all newborns

For the overlap between birth weight and birth weight for gestational age/sex, 45.1% of LBW newborns were SGA and 48.1% of SGA newborns were LBW (Table 4.6). A strong overlap was observed between NBW and not-SGA: 87.9% of NBW newborns were not-SGA; 86.6% of not-SGA newborns were NBW

(Table 4.6). Approximately 45.1% of LBW versus 12.1% of NBW newborns were SGA, and 48.1% of SGA versus 13.4% of not-SGA newborns were LBW (Table 4.6). Kappa coefficient showed that the overlap between LBW and SGA was fair (κ: 0.32, 95% CI: 0.26, 0.38). A scatter plot of birth weight for gestational age/sex by birth weight is provided in Figure 4.7.

Table 4.6. Overlap between birth weight and birth weight for gestational age/sex in all newborns.

Birth weight for gestational age/sex	Birth weight	
	↓ <2500g (LBW)	↓ ≥2500g (NBW)
<10th centile (SGA) →	45.1% / 48.1%	12.1% / 51.9%
≥10th centile (Not SGA) →	54.9% / 13.4%	87.9% / 86.6%

Abbreviations: LBW, low birth weight; NBW, normal birth weight; SGA, small for gestational age.

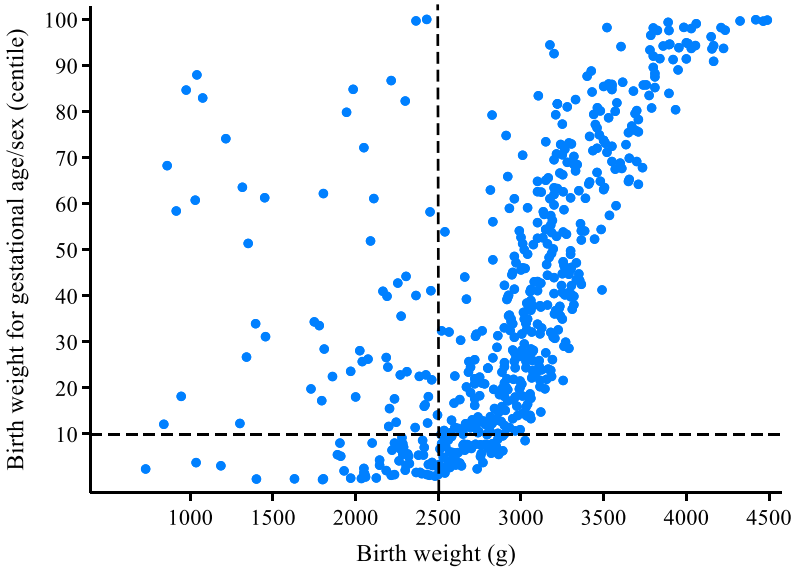


Figure 4.7. Scatter plot of birth weight for gestational age/sex by birth weight in all newborns. Dashed line, ruled line at cut-off points for defining low birth weight and small for gestational age, as appropriate.

4.4.3.2 Analysis by *in utero* HIV-exposure status

The overlap of birth weight and birth weight for gestational age/sex in the HIV-unexposed and HIV-exposed groups was similar (Table 4.7). In the HIV-unexposed group, 41.8% of LBW newborns were SGA and 48.3% of SGA newborns were LBW. There was a quite strong overlap between NBW and not-SGA: 89.7% of NBW newborns were not-SGA and 87% of not-SGA newborns were NBW (Table 4.7A). Approximately 41.8% of LBW versus 10.3% of NBW newborns were SGA; 48.3% of SGA versus 13% of not-SGA newborns were LBW (Table 4.7A). In the HIV-exposed group, 50% of LBW newborns were SGA and 47.9% of SGA newborns were LBW. There was a quite strong overlap between NBW and not-SGA: 84.7% of NBW newborns were not-SGA and 85.7% of not-SGA newborns were NBW (Table 4.7B). Approximately 50% of LBW versus 15.3% of NBW newborns were SGA; 47.9% of SGA versus 14.3% of not-SGA newborns were LBW (Table 4.7B). Kappa coefficients indicated that the overlap between LBW and SGA was fair in both groups: HIV-unexposed (κ: 0.33, 95% CI: 0.21, 0.46) and HIV-exposed (κ: 0.34, 95% CI: 0.19, 0.49). Scatter plots of birth weight for gestational age/sex by birth weight in the HIV-unexposed and HIV-exposed groups are presented in Figure 4.8.

Table 4.7. Overlap between birth weight and birth weight for gestational age/sex in HIV-unexposed (A) and HIV-exposed newborns (B).

A.

Birth weight for gestational age/sex	Birth weight	
	↓ <2500g (LBW)	↓ ≥2500g (NBW)
<10th centile (SGA) →	41.8% / 48.3%	10.3% / 51.7%
≥10th centile (Not SGA) →	58.2% / 13.0%	89.7% / 87.0%

Abbreviations: LBW, low birth weight; NBW, normal birth weight; SGA, small for gestational age.

B.

Birth weight for gestational age/sex	Birth weight	
	↓ <2500g (LBW)	↓ ≥2500g (NBW)
<10th centile (SGA) →	50.0% / 47.9%	15.3% / 52.1%
≥10th centile (Not SGA) →	50.0% / 14.3%	84.7% / 85.7%

Abbreviations: LBW, low birth weight; NBW, normal birth weight; SGA, small for gestational age.

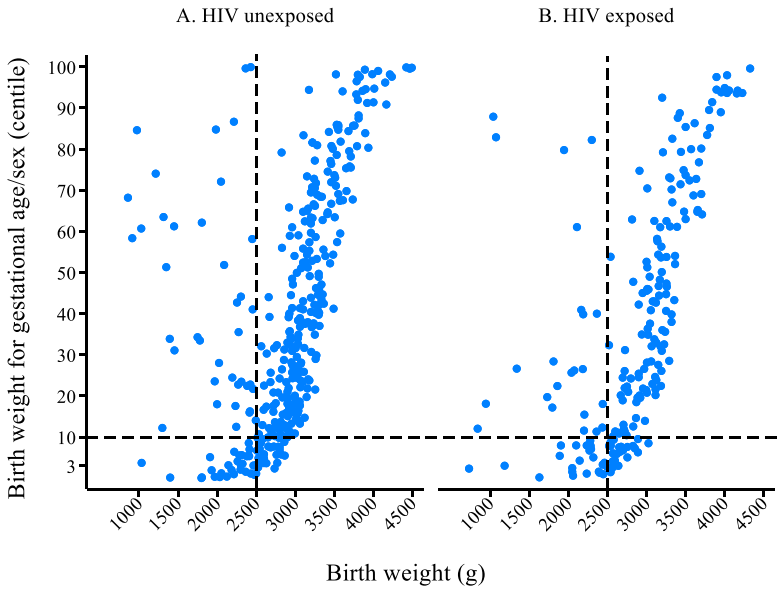


Figure 4.8. Scatter plots of birth weight for gestational age/sex by birth weight in HIV-unexposed (A) and HIV-exposed newborns (B). Dashed line, ruled line at cut-off points for defining low birth weight and small for gestational age, as appropriate.

4.5 Discussion

The overlap analyses in all newborns showed a substantial agreement for PTB and LBW, with poor agreement for PTB and SGA, and fair agreement for LBW and SGA. Overall, the findings of the overlap analyses in HIV-unexposed and HIV-exposed newborns were similar to those observed in all newborns, except for the overlap between PTB and SGA: there was poor agreement in the HIV-unexposed group and slight agreement in the HIV-exposed group.

To my knowledge, this is the first overlap analysis in which gestational age and birth weight were accurately measured, and birth weight for gestational age/sex was classified using an international standard [442]. The comparison of the present findings with previous findings was hampered by the limited number of existing studies. The agreement for the overlap between PTB and LBW in the present study (substantial) is higher than that observed by the previous study (moderate) [454]. However, for the overlap between PTB and SGA, the present study showed a lower agreement than that observed previously (poor versus slight) [454]. The present study is consistent with the previous study [454] for the overlap between LBW and SGA, i.e. there was fair agreement. Nevertheless, in the previous study [454], data were collected retrospectively, and gestational age and birth weight were measured using less accurate methods. These might have resulted in measurement error and misclassification of perinatal outcomes.

Substantial agreement between PTB and LBW in the present study suggests that the majority of LBW newborns were preterm and vice versa; thus, it might not be worthwhile to analyse these two perinatal outcomes separately. However, this

finding should not be interpreted as the potential use of birth weight as a proxy for gestational age. LBW has been most commonly used as a target for public health interventions [252,462], and the World Health Organization (WHO) has targeted an ambitious 30% reduction in LBW prevalence by 2025 in an attempt to reduce infant mortality [463]. This strategy relies upon several assumptions. First, LBW is a powerful predictor for infant mortality [238,251,252,452,453,464], and this has led to the notion that LBW is on the causal pathway of infant mortality. Second, LBW can be caused by PTB and/or IUGR; thus, in principle, LBW is preventable. Third, birth weight data are more accessible than gestational age, especially in LMICs [444,452,465], and are free through vital statistics or birth certificates [251,252,453]. Fourth, infant mortality is a rare event; thus, a more prevalent proxy is needed in order to observe a meaningful effect of a public health intervention on reducing infant mortality. With the wide availability of free birth weight data, LBW seems to be able to meet this need nicely. Therefore, any intervention that succeeds in reducing LBW is assumed to reduce infant mortality.

An assumption that LBW is an effective proxy for infant mortality risk suggests that populations with a higher proportion of LBW should have a higher rate of infant mortality than those with less LBW. Nevertheless, this is not always true: for example, as shown in the study assessing the association between maternal smoking and pregnancy outcomes [466]. The incidence of LBW was significantly higher in babies born to smoking than non-smoking mothers. However, the LBW babies born to smoking mothers showed a lower mortality rate than LBW babies born to non-smoking mothers – the so-called LBW paradox [466]. The LBW paradox was also found in studies comparing African-American versus White

babies [253], twins versus singletons [255], babies born at high versus low altitude [254], etc. Given the frequency distribution of birth weight is unique for each population, the dichotomy of birth weight (<2500g and ≥2500g) oversimplifies its association with infant mortality, thus resulting in the LBW paradox [251].

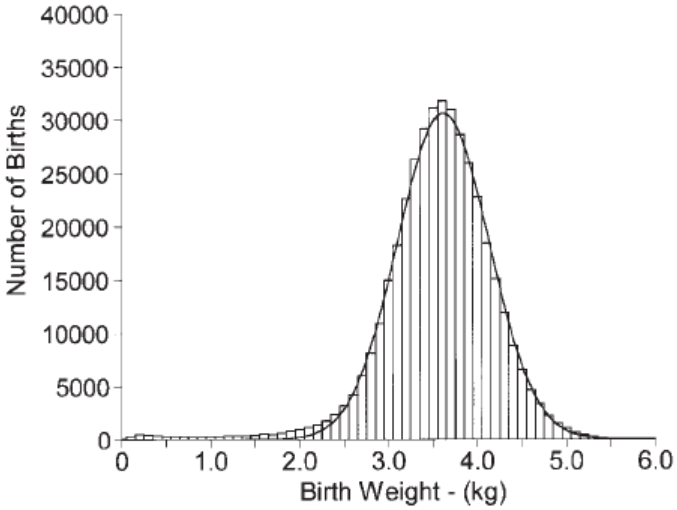


Figure 4.9. Birth weight distribution comprises the predominant and residual distribution (Wilcox et al. [251]). The predominant distribution is normal, and defined by its mean and standard deviation; this distribution estimates the vast majority of healthy term infants. The residual distribution is an extension in the lower tail of the predominant distribution, and defined by its proportion; this distribution estimates small and preterm infants.

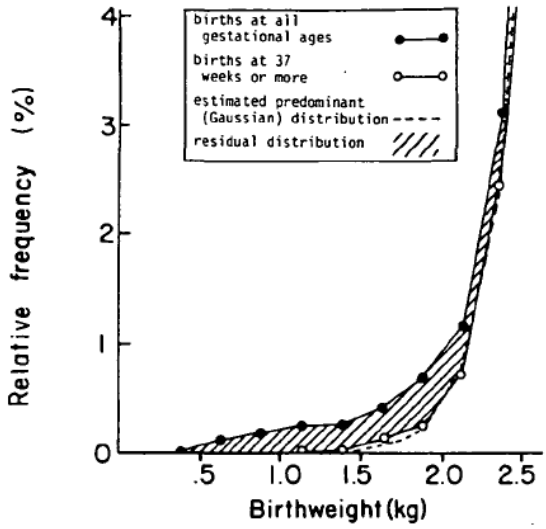


Figure 4.10. The distribution of births at term (o–o–o) is closely approximated by the predominant distribution (- - - -) (Wilcox et al. [467]).

According to Wilcox et al. [251,467], birth weight distribution consists of two components: predominant and residual distribution (Figure 4.9). The predominant distribution is characterised by a normal Gaussian (bell-shaped) distribution, and defined by its mean and standard deviation (SD) (Figure 4.9). The residual distribution is an extension in the lower tail of the predominant distribution, and defined by its proportion (Figure 4.9). The predominant distribution is very similar to the distribution of births at term, ≥37 weeks' gestation (Figure 4.10). Therefore, the predominant distribution estimates the birth weight distribution of the vast majority of healthy term babies, whereas the residual distribution estimates small and preterm babies (Figure 4.9 and Figure 4.10) – those at highest risk of mortality. These suggest that populations with a lower mean of the predominant distribution do not necessarily have a higher rate of infant mortality. On the other hand, populations with a higher proportion of babies in the residual distribution do have a higher rate of infant mortality [251,467]. Figure 4.9 shows that LBW (<2500g) comprises all babies in the residual distribution and those in the lower tail of the predominant distribution. Thus, an increase in babies in the residual distribution will increase the proportion of LBW. However, based on the Figure 4.9, the proportion of LBW also increases with a decrease in the mean, or an increase in the SD of the predominant distribution. As mentioned above, changes in the predominant distribution – changes in its mean and SD – are not necessarily associated with changes in infant mortality. Therefore, the proportion of LBW is not a reliable surrogate indicator of infant mortality risk [251,467]. Wilcox et al. [468] have shown that PTB is a more powerful predictor of infant mortality than LBW; their findings suggest that interventions aimed at preventing

LBW may have little impact on infant mortality; however, the prevention of PTB would benefit babies of all birth weights.

The present finding of poor agreement between PTB and SGA indicates that the vast majority of preterm babies were not SGA and vice versa. This suggests that these two perinatal outcomes are distinct and might have different mechanistic pathways; it is therefore worthy to analyse PTB and SGA separately. The poor agreement between PTB and SGA should be reflected in the distinctiveness of risk factors for these two perinatal outcomes [454]. However, existing studies comparing risk factors for PTB versus SGA among women in the same populations have shown mixed findings regarding the distinctiveness of risk factors [447-449,469-472]. Several studies have shown that the majority of predictors of PTB were distinct from those of SGA [448,469-471]. For example, in a Portuguese study [470], of nine predictors associated with either PTB or SGA; only one was associated with both PTB and SGA (a history of chronic diseases), two were associated with PTB only (number of antenatal visits <3 and a history of PTB), and six were associated with SGA only (maternal height and weight, gestational weight gain, smoking, gestational age at the first antenatal visit and a history of termination of pregnancy). In contrast, other studies have shown that the majority of predictors of PTB were similar to those of SGA [447,449,472], suggesting that these predictors may increase the risks of PTB and SGA through independent mechanistic pathways [454]. For example in a study from Tanzania [449], six predictors were shown to be associated with either PTB or SGA; four were associated with both PTB and SGA (young maternal age, gestational age at the first antenatal visit, maternal stature and being first born),

and only one was associated with each PTB (socio-economic status) or SGA only (newborn sex). However, none of the above-mentioned studies used accurate methods to determine gestational age and birth weight [447-449,469-472].

The width of CIs was used to express statistical power in the present study because *post hoc* power calculations are generally regarded to be of limited use as they can be misleading in the interpretation of "negative" results [473,474]. In the analyses of all newborns, the overlaps between PTB and LBW (κ: 0.69, 95% CI: 0.63, 0.75), PTB and SGA (κ: -0.05, 95% CI: -0.10, -0.01), and LBW and SGA (κ: 0.32, 95% CI: 0.26, 0.38) showed relatively narrow CIs, suggestive of sufficient statistical power. Furthermore, the estimated kappa values and their CIs all indicated the same level of agreement. For example, for the overlap between PTB and LBW, the kappa value of 0.69 and the lower (0.63) and upper (0.75) bounds of the CI indicated substantial agreement. However, for the overlap analyses by *in utero* HIV-exposure status, the CIs were relatively wide: HIV-unexposed – PTB and LBW (κ: 0.65, 95% CI: 0.54, 0.75), PTB and SGA (κ: -0.08, 95% CI: -0.17, 0.00), and LBW and SGA (κ: 0.33, 95% CI: 0.21, 0.46); HIV-exposed – PTB and LBW (κ: 0.71, 95% CI: 0.59, 0.83), PTB and SGA (κ: 0.07, 95% CI: -0.08, 0.21), and LBW and SGA (κ: 0.34, 95% CI: 0.19, 0.49), i.e. suggestive of limited statistical power in these analyses. In addition, the estimated kappa values and their CIs indicated different levels of agreement. For example, for the overlap between PTB and SGA in HIV-exposed newborns, the kappa value of 0.07 indicated slight agreement; however, the lower (-0.08) and upper (0.21) bounds of the CI indicated poor and fair agreement, respectively.

4.5.1 Strengths and limitations

The present study has several strengths. First, the present study analysed prospectively collected data unlike the previous study [454] which analysed retrospective data. Second, gestational age and birth weight were accurately measured using first-trimester ultrasound [79] and direct standardised measurement within at least 24h of birth [455], and birth weight for gestational age/sex was classified using the international INTERGROWTH-21st Newborn Size Standards [442]. All these efforts were aimed at minimising measurement error and misclassification of perinatal outcomes.

Nevertheless, the present study also has several limitations. First, there was less statistical power in the overlap analyses by *in utero* HIV-exposure status, as evidenced by the wider CIs. Second, for the overlap between PTB and LBW, there was a potential risk of bias that fetal size might have influenced clinical decision making regarding the timing of delivery through labour induction or Cesarean section [475,476]. For example, if small fetuses at a given gestational age are more frequently delivered early, the overlap between PTB and LBW will be artificially inflated.

4.5.2 Implications of findings

The present findings provide several directions for future studies. First, when data on gestational age and birth weight are both available, the analysis of two independent perinatal outcomes – PTB and SGA – should be sufficient; however, the analysis of LBW is neither useful nor necessary. Thus, in the following chapters of this thesis, LBW will not be included in any analysis. When birth

weight is the only information available, the residual distribution should be estimated, as shown by Wilcox et al. [251,467]. Second, for the overlap between PTB and SGA, a higher agreement in HIV-exposed (slight) versus HIV-unexposed newborns (poor) deserves further investigation through larger studies with accurately determined perinatal outcomes.

Chapter 5: Associations of treated maternal HIV infection and timing of ART initiation with adverse perinatal outcomes.

5.1 Introduction

Of the estimated 1.3 million HIV-positive pregnant women, 91% live in sub-Saharan Africa [151,362]. South Africa has the highest number of HIV-positive people in the world [1]; 30% of pregnant women in South Africa are HIV-positive [350], of whom more than 97% now receive antenatal antiretroviral therapy (ART) [61].

In 2018, the World Health Organization (WHO) published interim guidelines recommending ART transition from efavirenz (EFV) to dolutegravir (DTG)-based ART for all HIV patients, including pregnant women [222]. However, clinical evidence of DTG safety in pregnancy is very limited [222]. The most recent Botswana study [477] indicated a possible association between neural-tube defect (NTD) and DTG-based ART, initiated pre-conception: the prevalence of NTDs in women on DTG was three times higher than in women not on DTG. This highlights the importance of post roll-out surveillance of birth outcomes, including for the current WHO-recommended EFV-based ART, which is currently used by the vast majority of HIV-positive pregnant women in the world [377], including those living in South Africa [353,354].

Chapter 3 summarised the clear benefits of ART in pregnancy for maternal health and prevention of mother-to-child transmission (PMTCT); however, the associations of maternal HIV/ART and timing of ART initiation with perinatal outcomes – such as preterm birth (PTB) and small for gestational age (SGA) – remain unclear, with inconsistent findings among existing studies [13,14,28,29,62,64,96,97,404]. The use of less accurate methods to estimate gestational age and birth weight might have contributed in part to this inconsistency. For gestational age estimation, first trimester ultrasound is the most accurate method [79]; however, studies evaluating perinatal outcomes in HIV settings in sub-Saharan Africa almost always use imprecise methods (Chapter 3 – Appendix 3.6: Table 3.1): last normal menstrual period (LNMP) [13-17,28-30,67,96,97,154,368,376,398,402-404,477], symphysis-fundal height (SFH) [13,15-17,29,30,96,97,376,397,402-404,477], newborn clinical assessment [13,30,368,400,478], or late fetal ultrasound [29,67,154,399]. In addition, birth weight measurements are often poorly performed and/or reported, and often simply captured from medical records [28,29]. These may lead to measurement error, misclassification of PTB and SGA and, in turn, biased estimates that may produce inconsistent findings regarding the effects of maternal HIV/ART [28,29,399,478] and timing of ART initiation [24,29] on perinatal outcomes.

This chapter compares the risk of adverse perinatal outcomes by maternal HIV status and timing of ART initiation through a prospective pregnancy cohort in Soweto, South Africa. Gestational age was estimated using first trimester ultrasound (<14 weeks' gestation), and birth weight measurement was performed in a standardised manner within 24h of birth.

5.2 Aim

This chapter aims to evaluate:

1. The associations of treated maternal HIV infection and timing of ART initiation with adverse perinatal outcomes among South African pregnant women with accurately determined gestational age and birth weight.

5.3 Methods

5.3.1 Study setting

The study was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa. This hospital implements the South African PMTCT guidelines (Figure 5.1). In 2013, the guidelines recommended immediate initiation of fixed-dose combination (FDC) of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) or lamivudine (3TC) and EFV, irrespective of CD4 count, with two postnatal options: 1) continue FDC as lifelong treatment if CD4 count ≤350 cells/mm^3 or WHO stage 3/4 disease; 2) stop FDC after the period of vertical transmission if CD4 count >350 cells/mm^3 or WHO stage 1/2 disease [351]. In 2015, South Africa implemented option B+ [352] and, since 2016, the "treat all" recommendations [353] (Figure 5.1). In October 2019, there was an update recommending an ART switch from EFV to DTG-based ART for stable pregnant women with viral load <50 copies/mL and gestational age >6 weeks [354]. During the study period (May 28, 2013 to July 20, 2016), the vast majority of HIV-positive pregnant women at CHBAH received FDC of TDF+FTC/3TC+EFV (Figure 5.1). Further information about the study setting is provided in Chapter 4.

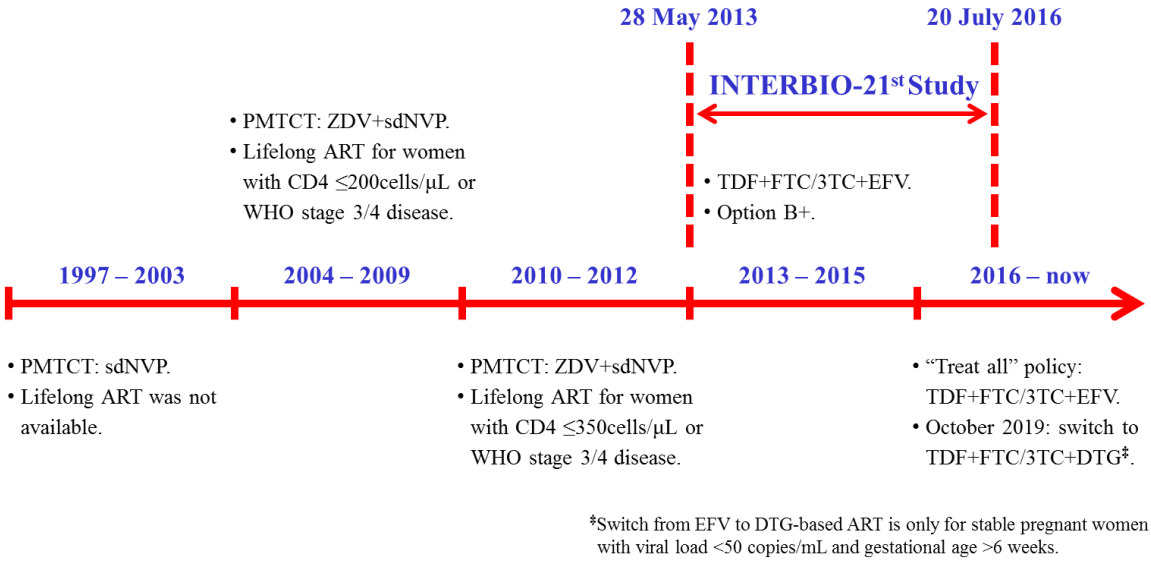


Figure 5.1. South African PMTCT guidelines implemented at Chris Hani Baragwanath Academic Hospital. Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; PMTCT, prevention of mother-to-child transmission; sdNVP, single dose nevirapine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; ZDV, zidovudine.

5.3.2 Study design

The present study analysed data collected by the INTERBIO-21st Study and "Soweto HIV and ART pregnancy study: the influence of HIV and antiretroviral treatment on pregnancy outcomes in Soweto, South Africa" (SHAPOSSA). The INTERBIO-21st Study is described in Chapter 4. SHAPOSSA itself is a prospective cohort aimed at assessing the association between maternal HIV/ART and perinatal outcomes, which was nested within the framework of the INTERBIO-21st Study at the Soweto study site.

5.3.3 Participants

Information on the study participants is provided in Chapter 4.

5.3.4 Data collection

A detailed description of the data collection periods in the INTERBIO-21st Study is provided in Chapter 4. Among pregnant women enrolled in the INTERBIO-21st Study, only HIV-positive women were enrolled in the SHAPOSSA Study, and enrolment was conducted at any follow-up visits or delivery. In the SHAPOSSA Study, women were consented to provide detailed information on HIV and ART, including clinical stage of HIV disease, use of ART, ART regimens, timing of ART initiation and antenatal CD4 counts.

5.3.5 Exposures of interest

The exposures of interest included treated maternal HIV infection and timing of ART initiation, which were captured from direct interviews, medical records and/or antenatal cards.

5.3.5.1 Maternal HIV infection

Newborns were considered to be: 1) HIV-exposed with evidence of a positive maternal HIV test or 2) HIV-unexposed with evidence of a negative maternal HIV test either before or during pregnancy.

5.3.5.2 Timing of ART initiation

Among HIV-positive mothers, if ART was initiated before the estimated date of conception, newborns were classified as exposed to pre-conception ART. However, if ART was initiated after the estimated date of conception, newborns were classified as exposed to post-conception ART.

5.3.6 Outcomes of interest

5.3.6.1 Definitions

5.3.6.1.1 Primary outcomes

The primary outcomes of interest were the composite outcomes "any adverse perinatal outcome" and "severe adverse perinatal outcome". Any adverse perinatal outcome included stillbirth, PTB, SGA or neonatal death (NND). Severe adverse perinatal outcome included stillbirth, very PTB (VPTB), very SGA (VSGA) or NND. Stillbirth was defined as a birth ≥24 weeks' gestation without any signs of life. The definitions of PTB and SGA are provided in Chapter 4. VPTB was defined as a live birth <32 weeks' gestation. VSGA was defined as a live birth <3rd centile of the INTERGROWTH-21st Newborn Size Standards [442]. NND was defined as an infant death in the first 28 days of life among babies who had never left the hospital.

5.3.6.1.2 Secondary outcomes

The secondary outcomes included newborn HIV infection and congenital abnormality. A positive newborn HIV test before hospital discharge, which was captured from the medical records, was used as evidence of HIV infection. Congenital abnormality was defined as any fetal abnormalities observed on ultrasound examination, and/or any neonatal abnormalities observed at birth.

5.3.6.2 Measurements

A detailed description of the gestational age and birth weight measurements is provided in Chapter 4.

5.3.7 Potential confounders

The potential confounders included maternal socio-demographic and nutritional characteristics, obstetric history, conditions related to the current pregnancy and HIV-related characteristics.

5.3.7.1 Definitions

5.3.7.1.1 Socio-demographic and nutritional characteristics

Socio-demographic and nutritional characteristics included maternal age, education, marital status, smoking, alcohol consumption, illicit drugs use, socio-economic status (SES) and pre-pregnancy body mass index (BMI). Maternal age was defined as the woman's age at the time of her last birthday, and analysed as a continuous variable (years). Maternal education was defined as the total number of years that the woman spent in formal education, and analysed as a continuous variable. Marital status was a binary variable: single or married/cohabiting. Single included those who had never been married and did not live with a partner, or who were widowed, separated or divorced. Smoking, alcohol and illicit drug use were a binary variable (yes/no) – whether or not the woman smoked, consumed alcohol and used illicit drugs during the pregnancy. SES was determined using asset-based measures at household level categorised as low, middle and high using a wealth index score generated from multiple correspondence analysis [479,480]. Pre-pregnancy BMI was calculated by dividing pre-pregnancy weight by the square of height, and analysed as a continuous variable (kg/m^2). If pre-pregnancy weight was not available, weight measured at enrolment (<14 weeks' gestation) was used. Maternal weight and height were measured directly (see below, 5.3.7.2

Measurements), the remaining variables were captured from direct interviews and/or medical records.

5.3.7.1.2 Obstetric history

Obstetric history included parity, number of previous miscarriages and history of adverse perinatal outcomes. Parity was a binary variable: parous if the woman had given birth >24 weeks' gestation irrespective of the outcome (live or stillborn), otherwise nulliparous. Number of previous miscarriages was categorised as 0–1 and ≥2 miscarriages. History of adverse perinatal outcomes was a binary variable (yes/no) – whether or not the woman had a history of termination of pregnancy, stillbirth, PTB or NND. Nulliparous women were always coded as "no" for the history of stillbirth, PTB and NND. Information on obstetric history was extracted from direct interviews and/or medical records.

5.3.7.1.3 Conditions related to the pregnancy

Conditions related to the pregnancy included gestational weight gain (GWG), acute infections (malaria, syphilis, genital tract/sexually-transmitted infections), gestational hypertension, haemoglobin levels across pregnancy trimesters and mode of delivery. GWG was calculated as the rate of GWG per week (kg/week), and categorised into three groups based on the 2009 Institute of Medicine (IOM) recommendations [481]: 1) inadequate (<0.44 for underweight, <0.35 normal weight, <0.23 overweight, <0.17 obese); 2) adequate (0.44–0.58 for underweight, 0.35–0.50 normal weight, 0.23–0.33 overweight, 0.17–0.27 obese); 3) excessive (>0.58 for underweight, >0.50 normal weight, >0.33 overweight, >0.27 obese). Malaria, syphilis and genital tract/sexually-transmitted infections were a binary

variable – whether or not the woman was diagnosed with or treated for malaria, syphilis and genital tract/sexually-transmitted infections during the pregnancy. Gestational hypertension was a binary variable (yes/no), defined as a clinical diagnosis of pregnancy-induced hypertension (PIH), preeclampsia, severe preeclampsia, eclampsia, or haemolysis and elevated liver enzymes and low platelet count (HELLP) syndrome with the onset >20 weeks' gestation in a previously normotensive woman. The definitions of gestational hypertensive disorders are provided in Table 5.1. Haemoglobin levels in the first, second and third trimester were defined as the lowest haemoglobin levels measured at <15, 15–27 and >27 weeks' gestation, respectively. Mode of delivery was a binary variable: vaginal delivery or Caesarean section. Maternal weight and blood pressure were measured directly (see below, 5.3.7.2 Measurements), the remaining variables were captured from the medical records.

Table 5.1. Definitions of gestational hypertensive disorders.

Features	PIH	Preeclampsia	Severe preeclampsia	Eclampsia	HELLP
Hypertension[§]	Mild	Mild	Severe	Mild/severe	Mild/severe
Proteinuria	Absent	Present	Present	Present	Present
Grand mal seizures	Absent	Absent	Absent	Present	May present
Haemolysis	Absent	Absent	Absent	Absent	Present
↑ liver enzymes	Absent	Absent	Absent	Absent	Present
Thrombocytopenia	Absent	Absent	Absent	Absent	Present

[§] Mild: >140/90 mmHg, severe: ≥160 mmHg systolic and/or ≥110mmHg diastolic.
Abbreviations: HELLP, haemolysis, elevated liver enzymes and low platelet count; PIH, pregnancy-induced hypertension.

5.3.7.1.4 HIV-related characteristics

HIV-related characteristics consisted of clinical stage of HIV disease, ART regimen and CD4 count during pregnancy. These characteristics were included in the analysis assessing the association between timing of ART initiation and

perinatal outcomes. Clinical stage of HIV disease was classified as stage 1 to 4 according to the WHO classification system. ART regimen was a binary variable: zidovudine (ZDV) monotherapy and highly active antiretroviral therapy (HAART). The first CD4 count measured during pregnancy was used, and analysed as a continuous variable (cells/mm^3). Clinical stage of HIV disease and ART regimen were extracted from the medical records and/or antenatal cards; antenatal CD4 count was obtained from the National Health Laboratory Service (NHLS), South Africa.

5.3.7.2 Measurements

5.3.7.2.1 Maternal weight and height

Maternal weight and height were measured directly at enrolment; afterwards, only maternal weight was measured at each follow-up visit. The measurements were performed by a trained anthropometrist using standardised techniques and equipment. Maternal weight was measured using a Seca™ 877 Scale (Seca, Germany) accurate to the nearest 100g. Maternal height was measured using a Seca™ Stadiometer 242 (range 62–210 cm) (Seca, Germany) with an accuracy of ±2mm. The equipment was calibrated at least twice weekly and maintained in a standardised manner.

5.3.7.2.2 Maternal blood pressure

Maternal blood pressure was measured from the right arm (whilst sitting) at study enrolment and each follow-up visit using the Microlife™ Blood Pressure Monitor for pregnant women (Microlife AG, Switzerland).

5.3.8 Statistical analysis

Maternal/newborn characteristics and adverse perinatal outcomes were compared by maternal HIV status (HIV-negative versus HIV-positive), and by timing of ART initiation (pre-conception versus post-conception ART) among the HIV-positive group. Continuous variables were compared using two-sample t-test or Wilcoxon-Mann-Whitney test, as appropriate. Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. The proportions of any adverse perinatal outcome, severe adverse perinatal outcome and stillbirth were calculated among all live and non-live newborns. The proportions PTB, VPTB, SGA, VSGA and NND were calculated among live newborns only. Statistical analyses were performed using STATA™ version 15.1 (StataCorp, Texas, USA). All statistical tests were two-sided with *P* value <0.05 was considered to be statistically significant.

5.3.8.1 Univariable analysis

The unadjusted associations of treated maternal HIV infection and timing of ART initiation with perinatal outcomes were examined using simple logistic regression. Unadjusted odds ratio (OR) and 95% confidence interval (CI) were reported as an effect estimate.

5.3.8.2 Multivariable analysis

Multiple logistic regression was used to assess the associations of treated maternal HIV infection and timing of ART initiation with perinatal outcomes controlling for potential confounders. The confounders were defined *a priori* based on the existing literature showing a consistent association between these confounders

and adverse perinatal outcomes [15,482-485]. Furthermore, a number of confounders were identified in the present study, including maternal education, marital status and SES. Two models were generated for each perinatal outcome. The first model (model 1) adjusted for socio-demographic and nutritional characteristics (maternal age, education, marital status, smoking, alcohol consumption, SES and pre-pregnancy BMI) and obstetric history (parity, number of previous miscarriages and history of adverse perinatal outcomes). The second model (model 2) was model 1 with additional confounders related to the pregnancy (GWG, gestational hypertension, haemoglobin levels across trimester of pregnancy and mode of delivery). For the association between timing of ART initiation and perinatal outcomes, HIV-related characteristics (clinical stage of HIV diseases, ART regimen and antenatal CD4 count) were included in the models. Adjusted OR and 95% CI were reported as an effect estimate.

5.3.8.3 Effect modification

Effect modifications between maternal HIV status/timing of ART initiation and any covariates included in the models were explored by performing stratified analyses using Mantel-Haenszel method. Stratum-specific ORs and 95% CIs were estimated. To assess the significance of an effect modification, a chi-square test of homogeneity was used [486]. Significant effect modifications were examined in the models using the Wald test, and only those that remained significant after adjustment for covariates were retained in the models.

5.3.8.4 Missing data

Multiple imputation by chained equations (MICE) method was employed to handle missing data [487]. To envisage the imputed values, imputation models were generated for each primary outcome: any adverse perinatal outcome and severe adverse perinatal outcome. Effect modifications were passively imputed [487,488].

5.3.9 Ethical considerations

A description of the ethical considerations is provided in Chapter 4.

5.4 Results

5.4.1 Treated maternal HIV infection and perinatal outcomes

After excluding women who were lost to follow-up (n=36), withdrew participation (n=11) or miscarried (n=37), a total of 596 women were included in the analyses: 376 (63.1%) were HIV-negative and 220 (36.9%) HIV-positive (Figure 5.2). In the HIV-negative group, live births were reported in 364 women: all had information on gestational age, and 360 on birth weight. In the HIV-positive group, live births were reported in in 214 women: all had information on gestational age, and 210 on birth weight (Figure 5.2).

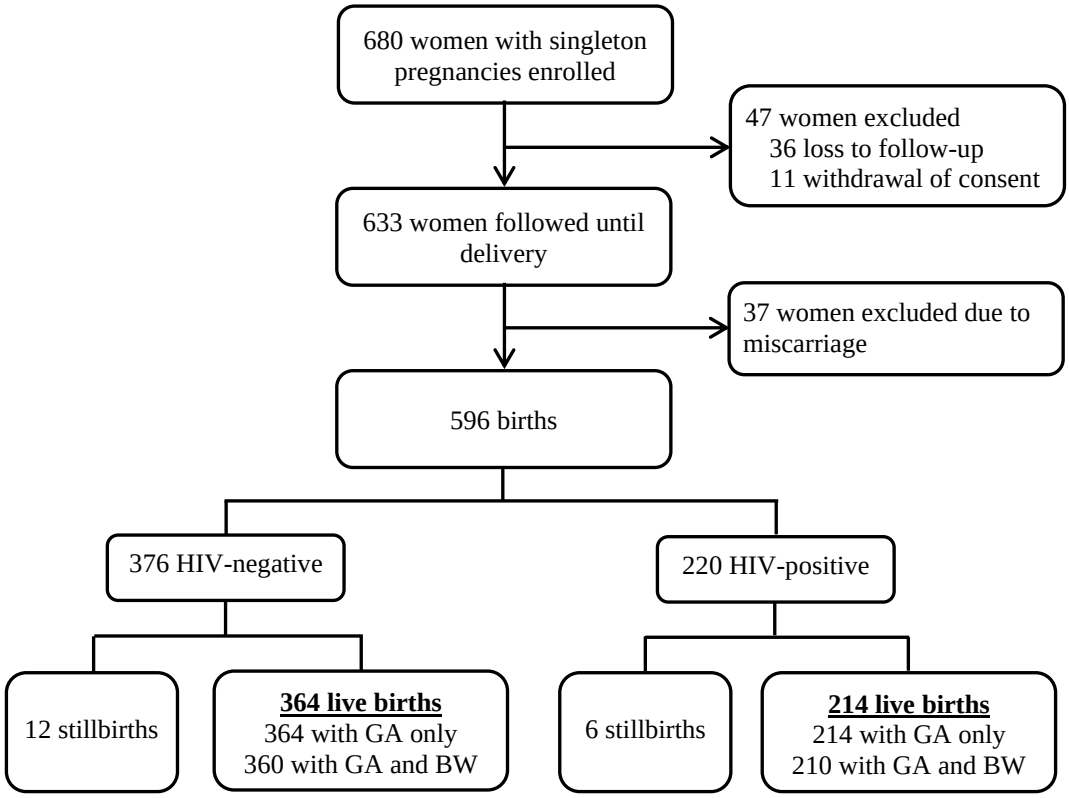


Figure 5.2. Flow diagram of the INTERBIO-21st Study participants. Abbreviations: BW, birth weight; GA, gestational age; HIV, human immunodeficiency virus.

The comparison of maternal characteristics by HIV status is presented in Table 5.2. HIV-positive women were older, less educated, more likely to be single and had a different distribution of SES compared to HIV-negative women. The proportion of parous women was higher in HIV-positive than HIV-negative group. However, the proportion of women with ≥2 previous miscarriages was higher in HIV-negative than HIV-positive group. In the second and third trimester, HIV-positive group had higher proportions of women with inadequate GWG, but lower haemoglobin levels compared to their HIV-negative counterparts. The comparison of newborn characteristics according to maternal HIV status is provided in Table 5.3.

Table 5.2. Maternal characteristics according to HIV status.

Maternal characteristics	**All women (N=596) n (%)**	**HIV-negative (N=376) n (%)**	**HIV-positive (N=220) n (%)**	***P* value[§]**
Age (years), median (IQR)	31 (26, 35.5)	30 (26, 34)	32 (28, 37)	<0.001
Education (years), median (IQR)	12 (11, 12)	12 (12, 12)	12 (11, 12)	<0.001
Single	362 (60.7)	216 (57.4)	146 (66.4)	0.031
Smoking	38 (6.4)	22 (5.8)	16 (7.3)	0.493
Alcohol consumption	49 (8.2)	27 (7.2)	22 (10)	0.227
Illicit drug use	3 (0.5)	1 (0.3)	2 (0.9)	0.558
Socio-economic status				
Low	115 (19.3)	77 (20.5)	38 (17.3)	0.020
Middle	262 (44)	149 (39.6)	113 (51.4)	
High	219 (36.7)	150 (39.9)	69 (31.4)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.7 (23.2, 30.1)	26.8 (23.5, 30.3)	26.4 (22.9, 30)	0.501
Nulliparity	90 (16.2)	66 (19)	24 (11.4)	0.018
Number of previous miscarriages ≥2	126 (21.1)	91 (24.2)	35 (15.9)	0.017
History of adverse perinatal outcomes	201 (33.7)	130 (34.6)	71 (32.3)	0.566
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (10.5, 13)	0.255
Number of antenatal care visits, median (IQR)	4 (2, 5)	4 (2, 5)	4 (2, 5)	1.000
GWG in the second trimester				
Inadequate	210 (35.8)	119 (32.3)	91 (42)	0.007
Adequate	130 (22.2)	77 (20.9)	53 (24.4)	
Excessive	246 (42)	173 (46.8)	73 (33.6)	
GWG in the third trimester				
Inadequate	164 (30)	94 (26.9)	70 (35.7)	0.024
Adequate	109 (20)	66 (18.9)	43 (21.9)	
Excessive	273 (50)	190 (54.2)	83 (42.4)	
Malaria	0	0	0	–
Syphilis	1 (0.2)	0	1 (0.5)	0.369
Genital tract/sexually-transmitted infections	8 (1.3)	3 (0.8)	5 (2.3)	0.152
Gestational hypertension	60 (10)	38 (10.1)	22 (10)	0.967

Table 5.2. Maternal characteristics according to HIV status (*continued from previous page*).

Maternal characteristics	All women (N=596) n (%)	HIV-negative (N=376) n (%)	HIV-positive (N=220) n (%)	*P* value[§]
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.2 ± 1.7	12.2 ± 1.7	12.1 ± 1.6	0.367
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.9 ± 1.5	12.1 ± 1.5	11.8 ± 1.5	0.026
Haemoglobin level in the third trimester (g/dL), mean ± SD	11.6 ± 1.7	11.8 ± 1.6	11.3 ± 1.7	<0.001
Caesarean section	338 (56.7)	212 (56.4)	126 (57.3)	0.832

[§] *P* value from t-test, Wilcoxon-Mann-Whitney, chi-square, or Fisher's exact test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
Missing data: <8%.
Abbreviations: BMI, body mass index; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

Table 5.3. Newborn characteristics according to maternal HIV status.

Newborn characteristics	All women (N=596) n (%)	HIV-negative (N=376) n (%)	HIV-positive (N=220) n (%)	*P* value[§]
Female	286 (48)	184 (48.9)	102 (46.4)	0.544
Gestational age at delivery (weeks), median (IQR)	38 (37, 39)	38.5 (37, 40)	38 (37, 39)	0.288
Birth weight (grams), median (IQR)	2990 (2595, 3260)	2995 (2650, 3265)	2962.5 (2540, 3255)	0.272
Birth weight for gestational age (centile), median (IQR)	33.5 (13.2, 63)	34.3 (15.2, 63.8)	31.1 (11.3, 61.2)	0.301

[§] *P* value from Wilcoxon-Mann-Whitney or chi-square test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
Missing data: <5%.
Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

Among the 596 women included in the analysis, 207 (34.7%) had babies with an adverse perinatal outcome and 74 (12.4%) with a severe adverse perinatal outcome. The proportions of any adverse perinatal outcome (39.1% versus 32.2%) and severe adverse perinatal outcome (13.6% versus 11.7%) were higher in HIV-

positive than in HIV-negative group. For specific perinatal outcomes, with the exception of stillbirth, the proportions were also higher in HIV-positive than in HIV-negative group (Table 5.4 and Figure 5.3).

Table 5.4. Adverse perinatal outcomes according to maternal HIV status.

Adverse perinatal outcomes	All women (N=596) n (%)	HIV-negative (N=376) n (%)	HIV-positive (N=220) n (%)	*P* value[§]
Any adverse perinatal outcome[ǀ]	207 (34.7)	121 (32.2)	86 (39.1)	0.087
Severe adverse perinatal outcome[¥]	74 (12.4)	44 (11.7)	30 (13.6)	0.490
PTB	99 (17.1)	56 (15.4)	43 (20.1)	0.147
VPTB	26 (4.5)	15 (4.1)	11 (5.1)	0.568
SGA	106 (18.7)	58 (16.2)	48 (23)	0.045
VSGA	30 (5.3)	17 (4.7)	13 (6.2)	0.446
Stillbirth	18 (3)	12 (3.2)	6 (2.7)	0.749
NND	9 (1.6)	2 (0.5)	7 (3.3)	0.015

[§] *P* value from chi-square or Fisher's exact test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
[ǀ] Any adverse perinatal outcome includes stillbirth, PTB, SGA and NND.
[¥] Severe adverse perinatal outcome includes stillbirth, VPTB, VSGA and NND.
Abbreviations: HIV, human immunodeficiency virus; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VPTB, very preterm birth; VSGA, very small for gestational age.

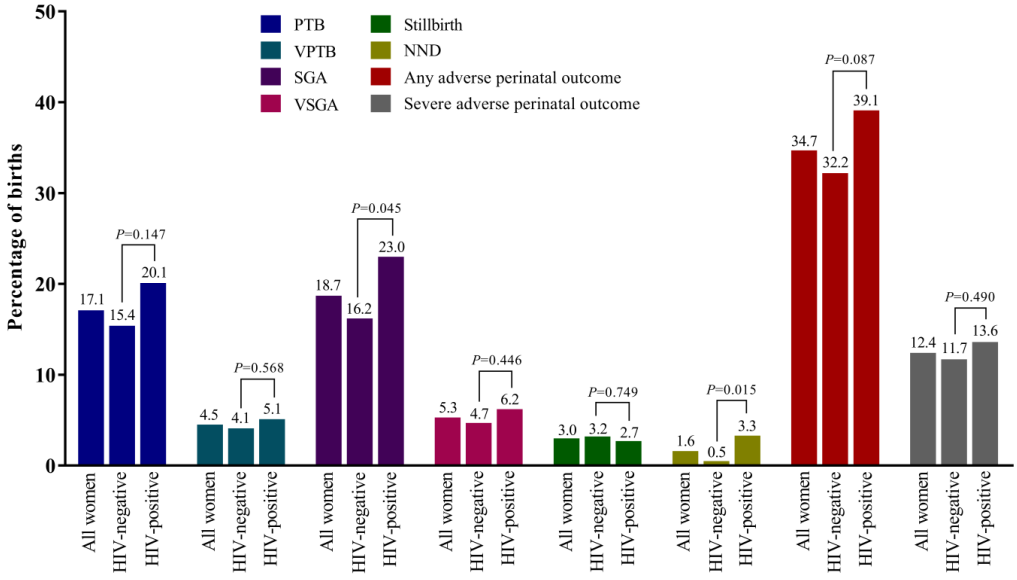


Figure 5.3. Proportions of composite and specific perinatal outcomes according to maternal HIV status. *P* values for comparisons are indicated on top of the bars (see Table 5.4). Abbreviations: HIV, human immunodeficiency virus; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VPTB, very preterm birth; VSGA, very small for gestational age.

5.4.1.1 Univariable analysis

In univariable analysis, treated maternal HIV infection was associated with an increased risk of any adverse perinatal outcome (OR: 1.35, 95% CI: 0.96, 1.91) with borderline statistical significance, but not associated with severe adverse perinatal outcome (OR: 1.19, 95% CI: 0.72, 1.96) (Table 5.5). For specific perinatal outcomes, only NND was significantly more common in treated HIV-positive women compared with HIV-negative women (OR: 6.15, 95% CI: 1.27, 29.88).

Table 5.5. Unadjusted and adjusted associations between treated maternal HIV infection and perinatal outcomes.

Adverse perinatal outcomes	OR (95% CI) for HIV-positive (reference: HIV-negative women)		
	Unadjusted	Adjusted	
		Model 1[§]	Model 2[ǀ]
Any adverse perinatal outcome	1.35 (0.96, 1.91)	1.45 (0.99, 2.12)	1.13 (0.72, 1.78)
Severe adverse perinatal outcome	1.19 (0.72, 1.96)	1.35 (0.79, 2.31)	0.84 (0.38, 1.82)

[§] Adjusted for maternal age, education, marital status, smoking, alcohol consumption, SES, pre-pregnancy BMI, parity, number of previous miscarriages, history of adverse perinatal outcomes.
[ǀ] Adjusted for all potential confounders in model 1, and GWG, gestational hypertension, haemoglobin levels across trimester of pregnancy and mode of delivery.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SES, socio-economic status.

5.4.1.2 Multivariable analysis

In model 1, after adjustment for socio-demographic, nutritional characteristics and obstetric history, the association between treated maternal HIV infection and an increased risk of any adverse perinatal outcome remained borderline significant (adjusted OR: 1.45, 95% CI: 0.99, 2.12) (Table 5.5). However, the association became non-significant (adjusted OR: 1.13, 95% CI: 0.72, 1.78) when additional confounders related to the pregnancy were included in model 2 (Table 5.5). NND

remained significantly associated with treated maternal HIV infection in model 1 (adjusted OR: 7.48, 95% CI: 1.35, 41.50), but not in model 2 (adjusted OR: 4.59, 95% CI: 0.65, 32.65).

5.4.1.3 Effect modification

In stratified analysis, maternal education was a significant effect modifier for the association between treated maternal HIV infection and any adverse perinatal outcome. Among women with ≤11 years of formal education, but not among those with >11 years, treated maternal HIV infection was associated with an increased risk of any adverse perinatal outcome. ORs and 95% CIs of this association varied across number of years of formal education (Figure 5.4). However, this effect modification became non-significant after adjustment for potential confounders in both model 1 and model 2; it was therefore excluded from the models. There was no statistically significant effect modifier for the association between treated maternal HIV infection and severe adverse perinatal outcome.

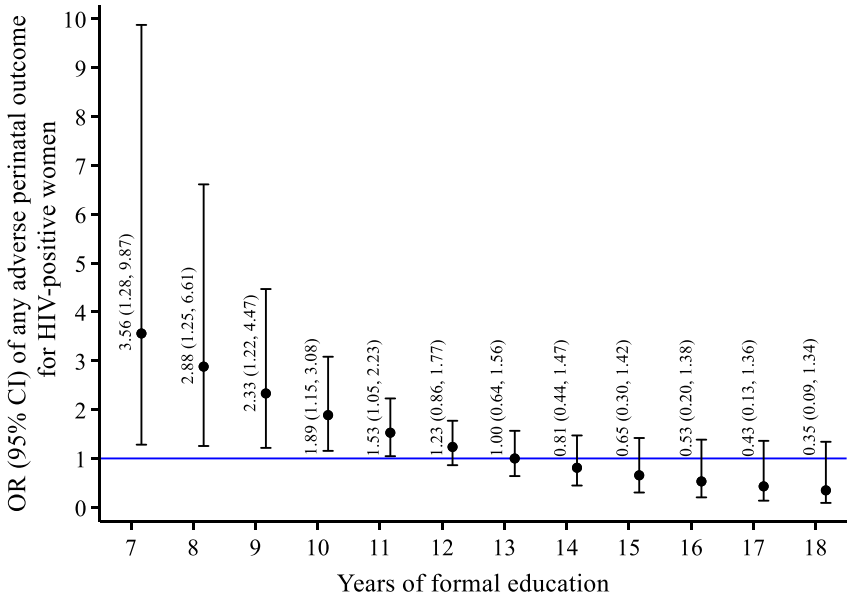


Figure 5.4. **Effects of treated maternal HIV infection on any adverse perinatal outcome across number of years of formal education**. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

5.4.1.4 Multiple imputation

From the 596 women included in the analysis, the rates of incomplete cases in model 1 and model 2 were 6.5% and 19.6%, respectively. In model 1, parity was the only variable with missing data (6.5%); in model 2, there were missing data for parity, GWG and haemoglobin levels across trimester of pregnancy, with the range of missing-data rates from 2.9% to 7.6%. Missing data in the present study were assumed as missing at random. Given that model 2 contained all variables in model 1 and additional variables related to the pregnancy, the imputation model was constructed by including all variables in model 2. No auxiliary variables were added to the imputation model. Number of imputations performed was 20 after considering the 19.6% of incomplete cases in model 2 [489]. Overall, the results of multivariable analyses based on complete-case and multiple imputation were comparable (Table 5.6).

Table 5.6. Adjusted associations between treated maternal HIV infection and perinatal outcomes based on complete-case versus multiple imputation.

Adverse perinatal outcomes	Adjusted OR (95% CI) for HIV-positive (reference: HIV-negative women)	
	Complete-case	Multiple imputation
Any adverse perinatal outcome		
Model 1[§]	1.45 (0.99, 2.12)	1.40 (0.97, 2.04)
Model 2[ǁ]	1.13 (0.72, 1.78)	1.24 (0.83, 1.85)
Severe adverse perinatal outcome		
Model 1[§]	1.35 (0.79, 2.31)	1.27 (0.75, 2.15)
Model 2[ǁ]	0.84 (0.38, 1.82)	1.19 (0.68, 2.07)

[§] Adjusted for maternal age, education, marital status, smoking, alcohol consumption, SES, pre-pregnancy BMI, parity, number of previous miscarriages, history of adverse perinatal outcomes.
[ǁ] Adjusted for all potential confounders in model 1, and GWG, gestational hypertension, haemoglobin levels across trimester of pregnancy and mode of delivery.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SES, socio-economic status.

5.4.2 Timing of ART initiation and perinatal outcomes

From the 220 HIV-positive women included in the analysis, 122 consented to participate in the SHAPOSSA Study (Figure 5.5). The comparison of maternal characteristics between HIV-positive women participating in the SHAPOSSA Study and those not participating is presented in Appendix 5.1: Table 5.1. Maternal characteristics were comparable between these two groups, except for the proportion of Caesarean delivery, which was higher in women participating in the SHAPOSSA Study compared with those not participating (63.9% versus 49%) (Appendix 5.1: Table 5.1).

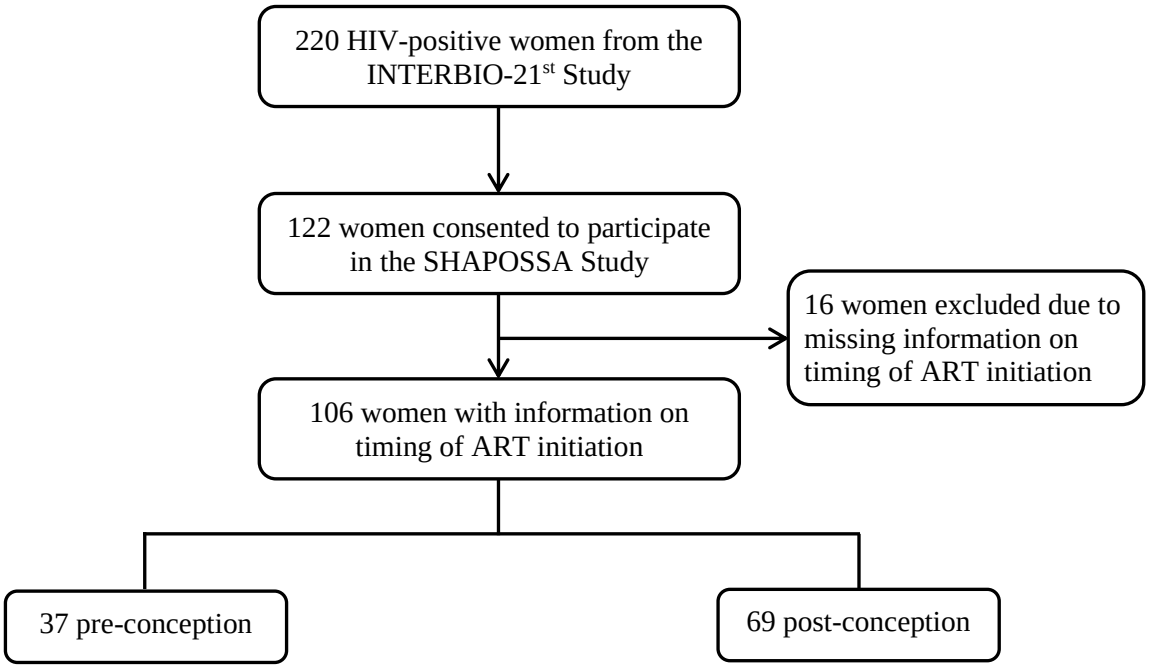


Figure 5.5. Flow diagram of the SHAPOSSA Study participants. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Of the 122 HIV-positive women participating in the SHAPOSSA Study, 106 had information on timing of ART initiation: 37 (34.9%) initiated ART pre-conception and 69 (65.1%) post-conception (Figure 5.5). The majority of these 106 women had stage 1 HIV disease (n=99; 96.2%), and received an FDC of TDF+FTC/3TC+EFV (n=88; 83%) (Table 5.7). The comparisons of maternal and newborn characteristics by timing of ART initiation are provided in Tables 5.8 and 5.9, respectively. HIV-positive women initiating ART pre-conception were older and had lower pre-pregnancy BMI than those initiating post-conception (Table 5.8). The proportion of female newborns was higher in women starting ART pre-conception than those starting post-conception (Table 5.9).

Table 5.7. Maternal HIV-related characteristics according to timing of ART initiation.

Maternal HIV-related characteristics	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[ǁ]
Clinical stage of HIV				
Stage 1	99 (96.2)	34 (97.1)	65 (95.6)	0.796
Stage 2	2 (1.9)	0	2 (2.9)	
Stage 3	2 (1.9)	1 (2.9)	1 (1.5)	
Stage 4	0	0	0	
ART regimen				
ZDV	2 (1.9)	0	2 (2.9)	<0.001
TDF+FTC/3TC+EFV (FDC)	88 (83)	24 (64.9)	64 (92.7)	
ZDV+3TC+EFV	5 (4.7)	2 (5.4)	3 (4.4)	
TDF+FTC+NVP	2 (1.9)	2 (5.4)	0	
TDF+3TC+LPV/r	9 (8.5)	9 (24.3)	0	
Antenatal CD4 count (cells/mm^3), median (IQR)	451 (320, 621)	462.5 (359, 498)	446 (312, 651)	0.892

[§] All HIV-positive women participating in the SHAPOSSA Study with information on timing of ART initiation.
[ǁ] *P* value from Wilcoxon-Mann-Whitney or Fisher's exact test, as appropriate, for comparisons between pre-conception and post-conception ART.
Missing data: <3%.
Abbreviations: ART, antiretroviral therapy; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; HIV, human immunodeficiency virus; IQR, interquartile range; LPV/r, lopinavir/ritonavir; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

Table 5.8. Maternal characteristics according to timing of ART initiation.

Maternal characteristics	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[ǁ]
Age (years), median (IQR)	32 (28, 37)	33 (31, 37)	30 (27, 35)	0.035
Education (years), median (IQR)	12 (11, 12)	12 (11, 12)	12 (11, 12)	0.729
Single	62 (58.5)	21 (56.8)	41 (59.4)	0.791
Smoking	7 (6.6)	2 (5.4)	5 (7.2)	1.000
Alcohol consumption	11 (10.4)	3 (8.1)	8 (11.6)	0.744
Illicit drug use	1 (0.9)	1 (2.7)	0	0.349

Table 5.8. Maternal characteristics according to timing of ART initiation (*continued from previous page*).

Maternal characteristics	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[‖]
Socio-economic status				
Low	17 (16)	6 (16.2)	11 (15.9)	0.994
Middle	51 (48.1)	18 (48.7)	33 (47.8)	
High	38 (35.9)	13 (35.1)	25 (36.3)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	27.2 (23.2, 30.0)	25.4 (22.6, 28.4)	28.4 (24.7, 30.8)	0.037
Nulliparity	13 (12.6)	2 (5.6)	11 (16.4)	0.133
Number of previous miscarriages ≥2	16 (15.1)	4 (10.8)	12 (17.4)	0.367
History of adverse perinatal outcomes	32 (30.2)	12 (32.4)	20 (29)	0.713
Gestational age at enrolment (weeks), median (IQR)	11 (10, 13)	11 (10, 13)	12 (10, 13)	0.699
Number of antenatal care visits, median (IQR)	4 (2, 5)	4 (2, 5)	4 (2, 5)	1.000
GWG in the second trimester				
Inadequate	45 (42.9)	17 (46)	28 (41.2)	0.878
Adequate	20 (19)	7 (18.9)	13 (19.1)	
Excessive	40 (38.1)	13 (35.1)	27 (39.7)	
GWG in the third trimester				
Inadequate	36 (37.5)	15 (44.1)	21 (33.9)	0.137
Adequate	19 (19.8)	9 (26.5)	10 (16.1)	
Excessive	41 (42.7)	10 (29.4)	31 (50)	
Malaria	0	0	0	–
Syphilis	0	0	0	–
Genital tract/sexually-transmitted infections	4 (3.8)	1 (2.7)	3 (4.4)	1.000
Gestational hypertension	9 (8.5)	2 (5.4)	7 (10.1)	0.490
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.4 ± 1.4	12.7 ± 1.4	12.2 ± 1.4	0.111
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.7 ± 1.5	11.7 ± 1.6	11.7 ± 1.5	0.903
Haemoglobin level in the third trimester (g/dL), mean ± SD	11.4 ± 1.6	11.4 ± 1.4	11.4 ± 1.7	0.869

Table 5.8. Maternal characteristics according to timing of ART initiation (*continued from previous page*).

Maternal characteristics	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[ǀ]
Caesarean section	72 (67.9)	25 (67.6)	47 (68.1)	0.954

[§] All HIV-positive women participating in the SHAPOSSA Study with information on timing of ART initiation.
[ǀ] *P* value from t-test, Wilcoxon-Mann-Whitney, chi-square, or Fisher's exact test, as appropriate, for comparisons between pre-conception and post-conception ART.
Missing data: <9%.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 5.9. Newborn characteristics according to timing of ART initiation.

Newborn characteristics	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[ǀ]
Female	48 (45.3)	22 (59.5)	26 (37.7)	0.032
Gestational age at delivery (weeks), median (IQR)	38 (37, 39)	38 (37, 39)	39 (37, 39)	0.369
Birth weight (grams), median (IQR)	3010 (2570, 3260)	2940 (2495, 3210)	3070 (2595, 3305)	0.304
Birth weight for gestational age (centile), median (IQR)	34.9 (10.9, 62.5)	34.9 (8.0, 53.8)	33.9 (11.4, 64.8)	0.690

[§] All HIV-positive women participating in the SHAPOSSA Study with information on timing of ART initiation.
[ǀ] *P* value from Wilcoxon-Mann-Whitney or chi-square test, as appropriate, for comparisons between pre-conception and post-conception ART.
Missing data: <3%.
Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

The proportions of the composite and most specific perinatal outcomes, except stillbirth and NND, were higher in women initiating ART pre-conception than those initiating post-conception (Table 5.10 and Figure 5.6).

Table 5.10. Adverse perinatal outcomes according to timing of ART initiation.

Adverse perinatal outcomes	All women[§] (N=106) n (%)	Pre-conception (N=37) n (%)	Post-conception (N=69) n (%)	*P* value[ǀ]
Any adverse perinatal outcome[¥]	37 (34.9)	15 (40.5)	22 (31.9)	0.373
Severe adverse perinatal outcome[‡]	10 (9.4)	4 (10.8)	6 (8.7)	0.737
PTB	19 (18.1)	9 (24.3)	10 (14.7)	0.221
VPTB	3 (2.9)	2 (5.4)	1 (1.5)	0.283
SGA	23 (22.3)	10 (27)	13 (19.7)	0.391
VSGA	6 (5.8)	3 (8.1)	3 (4.5)	0.664
Stillbirth	1 (0.9)	0	1 (1.4)	1.000
NND	3 (2.9)	1 (2.7)	2 (2.9)	1.000

[§] All HIV-positive women participating in the SHAPOSSA Study with information on timing of ART initiation.
[ǀ] *P* value from chi-square or Fisher's exact test, as appropriate, for comparisons between pre-conception and post-conception ART.
[¥] Any adverse perinatal outcome includes stillbirth, PTB, SGA and NND.
[‡] Severe adverse perinatal outcome includes stillbirth, VPTB, VSGA and NND.
Abbreviations: ART, antiretroviral therapy; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VPTB, very preterm birth; VSGA, very small for gestational age.

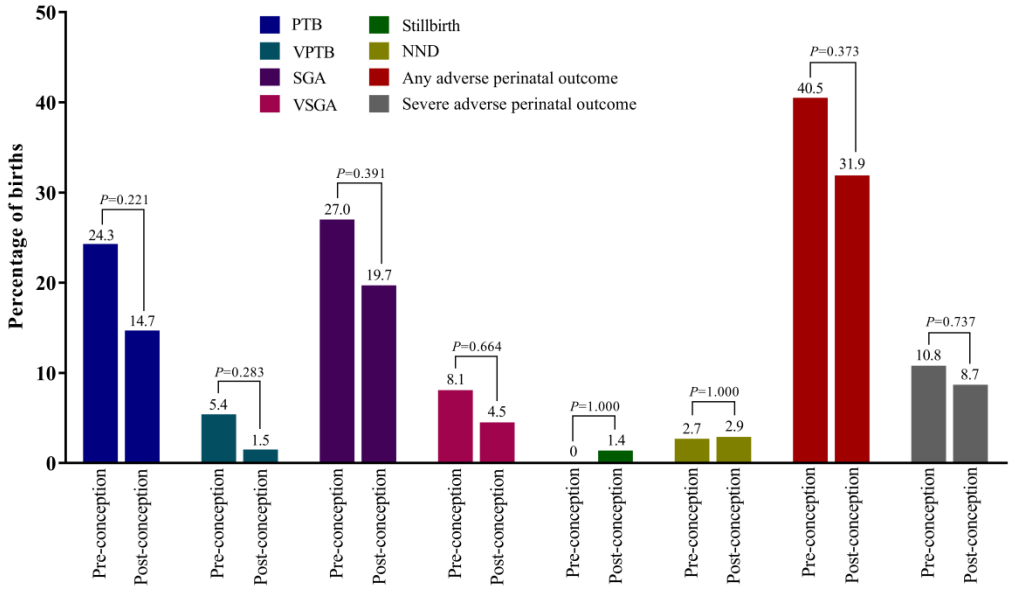


Figure 5.6. Proportions of composite and specific perinatal outcomes according to timing of ART initiation. *P* values for comparisons are indicated on top of the bars (see Table 5.10). Abbreviations: ART, antiretroviral therapy; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VPTB, very preterm birth; VSGA, very small for gestational age.

5.4.2.1 Univariable analysis

In univariable analysis, timing of ART initiation was not associated with any adverse perinatal outcome (OR: 1.46, 95% CI: 0.63, 3.34) or severe adverse perinatal outcome (OR: 1.27, 95% CI: 0.33, 4.83) (Table 5.11).

Table 5.11. Unadjusted and adjusted associations between timing of ART initiation and perinatal outcomes.

Adverse perinatal outcomes	OR (95% CI) for pre-conception (reference: post-conception ART)		
	Unadjusted	Adjusted	
		Model 1[§]	Model 2[ǁ]
Any adverse perinatal outcome	1.46 (0.63, 3.34)	0.97 (0.33, 2.81)	0.78 (0.17, 3.65)
Severe adverse perinatal outcome	1.27 (0.33, 4.83)	0.59 (0.07, 5.04)	–

[§] Adjusted for maternal age, education, marital status, smoking, alcohol consumption, SES, pre-pregnancy BMI, parity, number of previous miscarriages, history of adverse perinatal outcomes, clinical stage of HIV disease, ART regimen and antenatal CD4 count.
[ǁ] Adjusted for all potential confounders in model 1, and GWG, gestational hypertension, haemoglobin levels across trimester of pregnancy and mode of delivery.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SES, socio-economic status.

5.4.2.2 Multivariable analysis

After adjustment for potential confounders (including maternal HIV-related characteristics) in model 1, timing of ART initiation remained not associated with any adverse perinatal outcome (adjusted OR: 0.97, 95% CI: 0.33, 2.81) or severe adverse perinatal outcome (adjusted OR: 0.59, 95% CI: 0.07, 5.04) (Table 5.11). For any adverse perinatal outcome, the lack of association remained when additional confounders related to the pregnancy were included in model 2 (adjusted OR: 0.78, 95% CI: 0.17, 3.65) (Table 5.11). The adjusted analysis of model 2 for severe adverse perinatal outcome was not performed due to the limited number of outcome events (frequency).

5.4.2.3 Effect modification

Stratified analysis was not performed due to the small sample size as a result of limited consent being given.

5.4.2.4 Multiple imputation

Multiple imputation was not performed because it was hard to envisage the imputed values using this small sample size.

5.4.3 Secondary outcomes

There were no cases of newborn HIV infection. Overall, congenital abnormalities were observed in nine of the 596 (1.5%) births (Table 5.12). These abnormalities included hydronephrosis, hypotrophy of cerebrum, dilated ventricles, gastroschisis, narrow chest and disorganised pelvis, spina bifida (born to an HIV-positive woman initiating ART in the first trimester), malformation of lower limbs, club foot, polydactyly, ventricular septal defect and gross congenital malformation.

Table 5.12. Secondary outcomes according to maternal HIV status.

Secondary outcomes	All women (N=596) n (%)	HIV-negative (N=376) n (%)	HIV-positive (N=220) n (%)	*P* value[§]
HIV-positive newborn	0	0	0	–
Congenital abnormality	9 (1.5)	6 (1.6)	3 (1.4)	1.000

[§] *P* value from Fisher's exact test for comparisons between HIV-negative and HIV-positive women.
Abbreviation: HIV, human immunodeficiency virus.

5.5 Discussion

In this chapter, I have presented the results of a 3-year surveillance study of adverse perinatal outcomes in a country with the highest number of HIV-positive people in the world.

5.5.1 Treated maternal HIV infection and perinatal outcomes

The remarkable efficacy of antenatal ART in reducing vertical HIV transmission and improving maternal health is indisputable. The present study has shown that no newborns were diagnosed with HIV (Table 5.12); among the sub-group of HIV-positive women with ART information, 96.2% were asymptomatic of HIV disease (Table 5.7), with very few cases of acute co-infections (Table 5.8). However, the present study showed a borderline significant association between treated maternal HIV infection and an increased risk of any adverse perinatal outcome (adjusted OR: 1.45, 95% CI: 0.99, 2.12). This is slightly different from that observed in the Botswana study [96], which showed a significant association (adjusted RR: 1.40, 95% CI: 1.36, 1.44). The Botswana study [96] is a retrospective cohort that included 45,846 women: 34,138 HIV-negative and 11,708 HIV-positive on ART, almost 90% of whom received a combination of TDF+FTC+EFV. Nevertheless, in the Botswana study [96], gestational age was estimated using LNMP, late ultrasound, and/or SFH; birth weight was simply captured from the medical records, and the study was conducted at eight different hospitals with varied techniques and/or instruments to measure perinatal outcomes. These might have contributed to measurement error and misclassification of perinatal outcomes. In addition, only three potential

confounders – maternal age, education, gravidity – were included in the adjusted analysis [96].

Table 5.13. Hypothetical scenario of power calculations for future studies.

P_1	Differences in proportions of any adverse perinatal outcome ($P_2 - P_1$)									
	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%
10%	0.12	0.32	0.58	0.79	0.92	0.97	0.99	1	1	1
12%	0.11	0.29	0.52	0.74	0.89	0.96	0.99	1	1	1
14%	0.11	0.26	0.48	0.70	0.86	0.95	0.98	1	1	1
16%	0.10	0.24	0.45	0.67	0.83	0.93	0.98	0.99	1	1
18%	0.10	0.23	0.42	0.64	0.81	0.92	0.97	0.99	1	1
20%	0.10	0.21	0.40	0.61	0.78	0.90	0.96	0.99	1	1
22%	0.09	0.20	0.38	0.58	0.76	0.89	0.96	0.99	1	1
24%	0.09	0.19	0.36	0.56	0.75	0.87	0.95	0.98	1	1
26%	0.08	0.19	0.35	0.55	0.73	0.86	0.94	0.98	0.99	1
28%	0.08	0.18	0.34	0.53	0.71	0.85	0.94	0.98	0.99	1
30%	0.08	0.18	0.33	0.52	0.70	0.84	0.93	0.97	0.99	1
32%	0.08	0.17	0.32	0.51	0.69	0.83	0.93	0.97	0.99	1
34%	0.08	0.17	0.31	0.50	0.68	0.83	0.92	0.97	0.99	1
36%	0.08	0.16	0.31	0.49	0.67	0.82	0.92	0.97	0.99	1

P_1, proportion of any adverse perinatal outcome in HIV-negative; P_2, proportion in HIV-positive women.

The lack of significant associations between treated maternal HIV infection and adverse perinatal outcomes in the present study could be due to limited statistical power, as judged by the relatively wide CIs [473,474]. As illustration, Table 5.13 presents the power calculations for a future study with the same study characteristics and sample size as the present study: 596 women (376 HIV negative and 220 HIV-positive). P_1 and P_2 (Table 5.13) refer to the proportions of any adverse perinatal outcome in HIV-negative and HIV-positive women, respectively. In the Botswana study [96], the proportions of any adverse perinatal outcome in HIV-negative and HIV-positive women were 28.9% and 39.6%, respectively, i.e. the difference between these two proportions was around 11%.

From Table 5.13, it can be seen that, in a future study, if the proportions of any adverse perinatal outcome in the HIV-negative and HIV-positive women were 28% (P_1) and 40% (P_2), respectively, the power to detect a 12% difference between these two proportions would be 85%.

The present study population had low levels of smoking, alcohol consumption, illicit drug use and acute infections (malaria, syphilis and genital tract/sexually-transmitted infections) (Table 5.2). The proportions of underweight (BMI <18.5kg/m^2; HIV-negative: 2.1%; HIV-positive: 0.9%) and obese women (BMI ≥30kg/m^2; HIV-negative: 26.1%; HIV-positive: 25.5%) were comparable across maternal HIV status. In the light of the study design, women were scheduled for an antenatal care (ANC) visit every 5±1 weeks, median (IQR): 4 (2, 5) visits (Table 5.2). At each ANC visit, ultrasound measurements and maternal health examinations were performed. The majority of women took folic acid (n=573; 96.1%) and iron (n=542; 90.9%) supplementations during the pregnancy. With regard to treated maternal HIV infection, there are two major contributors to adverse perinatal outcomes: maternal health and ART-related effects. For maternal health, most HIV-positive women in this study were asymptomatic, with a median (IQR) of antenatal CD4 count 451 (320, 621) cells/mm^3 (Table 5.7). The vast majority of those women received ART, which has been associated with adverse perinatal outcomes through immunological [431,490] and hormonal mechanisms [425,491,492]. In HIV-positive pregnant women, ART has been shown to induce a T helper cell 2 (Th2) to T helper cell 1 (Th1) shift, resulting in increased Th1 and decreased Th2 responses [431]. These immunological changes are seen in preeclamptic women [491,493]. Furthermore, antenatal ART

(especially HAART) has been linked with higher levels of leptin – a hormone that plays a role in the pathophysiology of preeclampsia [491]. However, in the present study, the incidence of gestational hypertension (including preeclampsia) in treated HIV-positive women (10%) was comparable with that in HIV-negative women (10.1%) (Table 5.2). The use of PI-based ART in pregnancy has been associated with decreased progesterone concentrations that could lead to adverse perinatal outcomes [425]. Nevertheless, most HIV-positive women in the present study received an FDC of TDF+FTC/3TC+EFV (Table 5.7). In summary, good maternal health, routine ANC visits and high ART coverage may partly explain why the association between treated maternal HIV infection and adverse perinatal outcomes in the present study did not reach statistical significance.

The present study showed that, in the unadjusted analysis, maternal education was an effect modifier for the association between treated maternal HIV infection and any adverse perinatal outcome: treated maternal HIV infection was associated with any adverse perinatal outcome in women with ≤11 years of formal education, but not among those with >11 years (Figure 5.4). Although this effect modification became non-significant in the adjusted analyses (model 1 and model 2), this finding deserves further attention. In general populations, maternal education is one of the most powerful social determinants of maternal health and perinatal outcomes in both low and middle-income countries (LMICs) [494-498] and high-income countries [237,499-501]. Higher levels of education are expected to enhance the knowledge of a healthy lifestyle related to hygiene, nutrition and disease prevention [497,498,500,502]; contraceptive and ANC utilization [237,495-497], as well as HIV, ART and PMTCT [503-505]. Furthermore,

education is associated with women's employment and income, self-esteem and involvement in health-related decisions [237,496,502]. Table 5.2 in Appendix 5.2 presents the comparison of maternal characteristics according to HIV status, stratified by maternal education: ≤11 versus >11 years of education. Among women with ≤11 years of education, maternal characteristics were comparable across HIV status, except for maternal age and number of previous miscarriages ≥2; HIV-positive women were older and had a lower proportion of women with ≥2 previous miscarriages compared with HIV-negative women (Appendix 5.2: Table 5.2). However, these remain insufficient to explain why, in the unadjusted analysis, treated maternal HIV-infection increased the risk of any adverse perinatal outcome in women who spent ≤11 years in formal education. Limited information on maternal HIV/ART (Appendix 5.2: Table 5.3) was also insufficient to explain this finding.

The incidence of NND in HIV-positive women in the present study (3.3%) is higher than that observed in women receiving EFV (1.9%) [404], DTG (1.2%) [97,477], or NVP (1.9%) [96], but somewhat similar to women receiving LPV/r-based ART (2.8%) [96] in the Botswana studies. Conversely, the incidence of NND in HIV-negative women in the present study (0.5%) was relatively low, despite the high overall rate of adverse perinatal outcomes (Table 5.4 and Figure 5.3). This incidence is lower than that reported in HIV-negative women in the Botswana study (1.4%) [97]. The present finding of an association between treated maternal HIV infection and NND (adjusted OR: 7.48, 95% CI: 1.35, 41.50) is concerning, despite limited statistical power – as evidenced by the wide CI – due to the scarcity of outcome events. This association is consistent with the

Botswana study [96]. A previous South African study reported that the most common causes of NND are PTB-related complications [506]. Of the nine NNDs in the present study, eight were <28 weeks' gestation (six born to HIV-positive and two to HIV-negative women) and one was at 35 weeks' gestation (to an HIV-positive woman). Furthermore, all nine NNDs had a birth weight <1500g and were admitted to the intensive care unit. The effect of treated maternal HIV infection on other specific perinatal outcomes (PTB and SGA) is discussed in Chapter 6.

The incidence of congenital abnormalities in the present study was similar between HIV-negative (1.6%) and HIV-positive women (1.4%) (Table 5.12), despite most HIV-positive women commencing ART either pre-conception (n=37) or in the first trimester (n=56). This finding is similar to the results from a Ugandan study [507] and the Antiretroviral Pregnancy Registry [508]. However, the Botswana study [477], which only reported major external structural malformations, showed a lower incidence of congenital defects: 0.6% for each HIV-negative and HIV-positive group.

5.5.2 Timing of ART initiation and perinatal outcomes

Among women initiating ART pre-conception, the rate of any adverse perinatal outcome in the present study (40.5%) is higher than that observed in the Botswana study (36.7%) [404]. For severe adverse perinatal outcome, the present study (10.8%) showed a similar rate with that observed in the Botswana study (11.0%) [404]. Among women initiating ART post-conception, the rates of adverse

perinatal outcomes in the present study (any: 31.9%; severe: 8.7%) are lower than those observed in the Botswana study (any: 34.5%; severe: 11.1%) [97].

The present study showed no difference in the risk of adverse perinatal outcomes between women starting ART pre-conception and those starting post-conception. The finding is different from the meta-analysis in Chapter 3 and previous meta-analysis [64], which showed an association between pre-conception initiation of ART and an increased risk of PTB, VPTB, SGA and VSGA, especially in LMICs. The present finding of no association between timing of ART initiation and perinatal outcomes could be due to inadequate statistical power (as evidenced by the wide CIs), given the limited number of women who consented to provide information on HIV/ART, and the small number of outcome events.

Whilst the present study was unable to show a significant association, the rates of adverse perinatal outcomes were higher in women initiating ART prior to conception compared with those initiating post-conception (Table 5.10 and Figure 5.6). The effect of ART on vascular endothelium, which may lead to placental insufficiency, has been linked to an increased risk of adverse perinatal outcomes among women initiating ART pre-conception [509].

The reported associations between pre-conception ART and adverse perinatal outcomes [64], especially PTB, have raised concerns about the risk of selection bias. The women with post-conception initiation – who often start ART late in pregnancy, especially in African settings [13,97] – might not have had the same opportunity as women with pre-conception initiation to experience adverse events within a study, as these may have occurred prior to possible enrolment [438]. In

the present study, this concern was addressed by recruiting women very early (<14 weeks' gestation), thus minimising the risk of selection bias.

5.5.3 Strengths and limitations

The present study has several strengths. First, the methodological advantages offered by the INTERBIO-21st Study allowed me to perform the first-ever analysis in sub-Saharan Africa comparing adverse perinatal outcomes by maternal HIV status and timing of ART initiation, in which all women had a first trimester ultrasound scan, the most accurate method to date a pregnancy [79], which minimised misclassification of gestational age. Second, all women were recruited at <14 weeks' gestation and prospectively followed until delivery, which enabled the present study to capture adverse perinatal outcomes from an early gestational age. In sub-Saharan Africa, pregnant women commonly present late for ANC [13,97], which not only hampers accurate gestational age assessment but also leads to an underestimation of adverse perinatal outcomes in prospective studies, as these outcomes may have occurred prior to enrolment. Third, birth weight measurement was directly performed by trained anthropometrists within 24h of birth using standardised techniques and instruments, which minimised random measurement error and misclassification of birth weight. Fourth, SGA and VSGA were classified using the international INTERGROWTH-21st Newborn Size Standards [442], thereby enabling international comparison with other studies using the same standard [96,97,404,477]. Fifth, extrapolating from the sub-group with ART information, the population studied had high ART coverage and most women received EFV-based ART. This enabled the assessment of perinatal outcomes in HIV-positive women on WHO-recommended first-line ART, as

implemented in most affected countries in the world [377]. Sixth, congenital abnormality was assessed using both serial ultrasound examinations during follow-up visits and surface examination at birth. These allowed the assessments of both internal (brain, heart, gastro-intestinal, bladder, lungs/pleura and kidneys) and external abnormalities unlike the Botswana studies [97,477], which only relied on the newborn surface examination. Seventh, a large number (>200) of variables relating to socio-economic, medical and obstetric factors were collected through direct measurements, interviews, medical records, and/or antenatal cards. Data quality was very high with very few missing data: for example, only eight of 578 (1.4%) live newborns had missing birth weight data (Figure 5.2), which is a great achievement in a very busy hospital in a resource-limited setting.

Nevertheless, the present study has several limitations. The first was an inability to demonstrate causal inference due to the nature of the observational study (potential unmeasured confounding). Second, inadequate statistical power might have contributed to the borderline significant association between treated maternal HIV-infection and any adverse perinatal outcome. Third, the analysis of severe adverse perinatal outcome was limited by the rarity of outcome events, including VPTB, VSGA, stillbirth and NND. Fourth, not all HIV-positive women consented to provide detailed information on ART, which resulted in: 1) limited statistical power for the association between timing of ART initiation and perinatal outcomes and 2) an inability to compare perinatal outcomes by ART regimen. Fifth, for women without information on pre-pregnancy weight, maternal weight measured at enrolment (<14 weeks' gestation) was used to calculate pre-pregnancy BMI although the difference between maternal weight measured pre-

pregnancy and that measured at enrolment should be insignificant because the rate of GWG during the first trimester is low [481,510,511]. Sixth, NND was recorded at hospital discharge, i.e. NND outside the hospital was not documented. Seventh, the ascertainment of any congenital abnormalities presenting after a few days of life [512] was not performed. Eighth, miscarriage was not included in the present analysis (Figure 5.2) due to the risk of bias, as this outcome may have occurred <14 weeks' gestation. Ninth, ART adherence, tolerability and toxicity were not measured; however, no MTCTs were reported so it is reasonable to assume that the level of ART adherence was high in the present study. Finally, it may be difficult to generalise the present findings to other settings with different populations, risk factors, ART regimens and country-income status.

5.5.4 Implications of findings

The present findings should provide guidance for future ART surveillance and research. First, consistent with Chapter 3, ongoing ART surveillance in HIV-positive pregnant women remains crucial. It is imperative to optimise ART regimens during pregnancy to continue to improve maternal health and perinatal outcomes and associated neonatal/child morbidity and mortality, as well as to eliminate vertical HIV transmission. By early 2019, more than 75 LMICs had incorporated DTG in their national guidelines, and more than 35 LMICs had initiated procurement. To date, more than one million HIV-positive people (including pregnant women) are receiving DTG in LMICs [222]. Second, more, larger studies, including RCTs, are needed to assess properly the effects of treated maternal HIV infection, timing of ART initiation and different ART regimens on perinatal outcomes, especially for severe outcomes with rare events. Third, to

improve the reliability and comparability of future studies, they should recruit women at an early gestational age (<14 weeks); use first trimester ultrasound to estimate gestational age accurately; measure birth weight in a standardised manner within 24h of birth, and use the international INTERGROWTH-21st Newborn Size Standards [442] to classify SGA and VSGA. Fourth, further research is needed to investigate the biological mechanisms and potential risk factors for adverse perinatal outcomes among babies born to treated HIV-positive women.

Chapter 6: Risk factors for preterm birth and small for gestational age in all women, HIV-negative and HIV-positive women.

6.1 Introduction

Chapter 5 provided a prospective cohort analysis of South African pregnant women whose accurate gestational age and birth weight estimated using first trimester ultrasound and direct standardised measurement within 24h of birth. Treated maternal HIV infection was, with borderline statistical significance, associated with the composite "any adverse perinatal outcome" including stillbirth, preterm birth (PTB), small for gestational age (SGA) and neonatal death (NND). However, the associations between treated maternal HIV infection and specific perinatal outcomes (i.e. PTB and SGA), in which gestational age and birth weight were measured using the most accurate methods, have never been reported in sub-Saharan Africa.

Untreated maternal HIV infection characterised by poor maternal health has been shown to increase the risk of stillbirth, PTB, low birth weight (LBW) and SGA compared to HIV-negative pregnancies, especially in sub-Saharan Africa [365]. Whilst lifelong antiretroviral therapy (ART) in pregnancy has been implemented since 2004 (Chapter 5: Figure 5.1), PTB estimates have steadily increased in South Africa: 10.2% in 2005, 11.4% in 2010 and 12.4% in 2014 [6]. This suggests

that maternal HIV is not a single player that exclusively contributes to the occurrence of adverse perinatal outcomes. Meta-analyses in Chapter 3 indicate the possible involvement of antenatal ART in increasing the risk of PTB, spontaneous PTB, very PTB, LBW and SGA in HIV-positive compared to HIV-negative women. However, the contribution of maternal risk factors other than HIV and ART to adverse perinatal outcomes should not be overlooked. Studies investigating risk factors for PTB and SGA have been widely conducted in sub-Saharan Africa. However, most studies used less accurate methods to measure gestational age and birth weight, and included general populations or HIV-negative women [449,485,513-525]. Chapter 5 (Table 5.2) has shown that HIV-positive women were older, less educated, more likely to be single and parous, had a different distribution of socio-economic status (SES), had higher proportions of inadequate gestational weight gain (GWG) and lower haemoglobin levels compared to HIV-negative women. Given these different characteristics, it is therefore imperative to identify risk factors for PTB and SGA not only in the general population or HIV-negative women, but also in HIV-positive women because such risk factors could be different.

This chapter investigates risk factors for PTB and SGA in both all women and HIV-negative and HIV-positive women separately, using accurately determined gestational age and birth weight, in a resource-poor setting with the highest HIV prevalence globally, so as to provide guidance for targeting improvement of perinatal outcomes in both HIV-negative and HIV-positive women.

6.2 Aims

This chapter aims to investigate:

1. The associations between treated maternal HIV infection and PTB and SGA among South African pregnant women with accurately determined gestational age and birth weight.
2. Risk factors for PTB and SGA among South African women irrespective of HIV status, and separately among HIV-negative and HIV-positive women.

6.3 Methods

Descriptions of the study setting and design, participants, data collection and ethical considerations are provided in Chapters 4 and 5. Definitions of the perinatal outcomes of interest (PTB and SGA) are provided in Chapter 4. Descriptions of the potential risk factors, including treated maternal HIV infection, maternal age, education, marital status, pre-pregnancy BMI, parity, history of adverse perinatal outcomes, inadequate GWG, gestational hypertension and haemoglobin levels across pregnancy trimesters are provided in Chapter 5.

6.3.1 Statistical analysis

Statistical analyses were performed using STATA™ version 15.1 (StataCorp, Texas, USA). All statistical tests were two-sided; a *P* value <0.05 was considered to be statistically significant. The five main steps of statistical analyses performed in the present study are shown in Figure 6.1.

6.3.1.1 Univariable analysis

The unadjusted associations of each potential risk factor with PTB and SGA were examined using simple logistic regression (Figure 6.1). Unadjusted odds ratio (OR), 95% confidence interval (CI) and *P* values were reported as effect estimates.

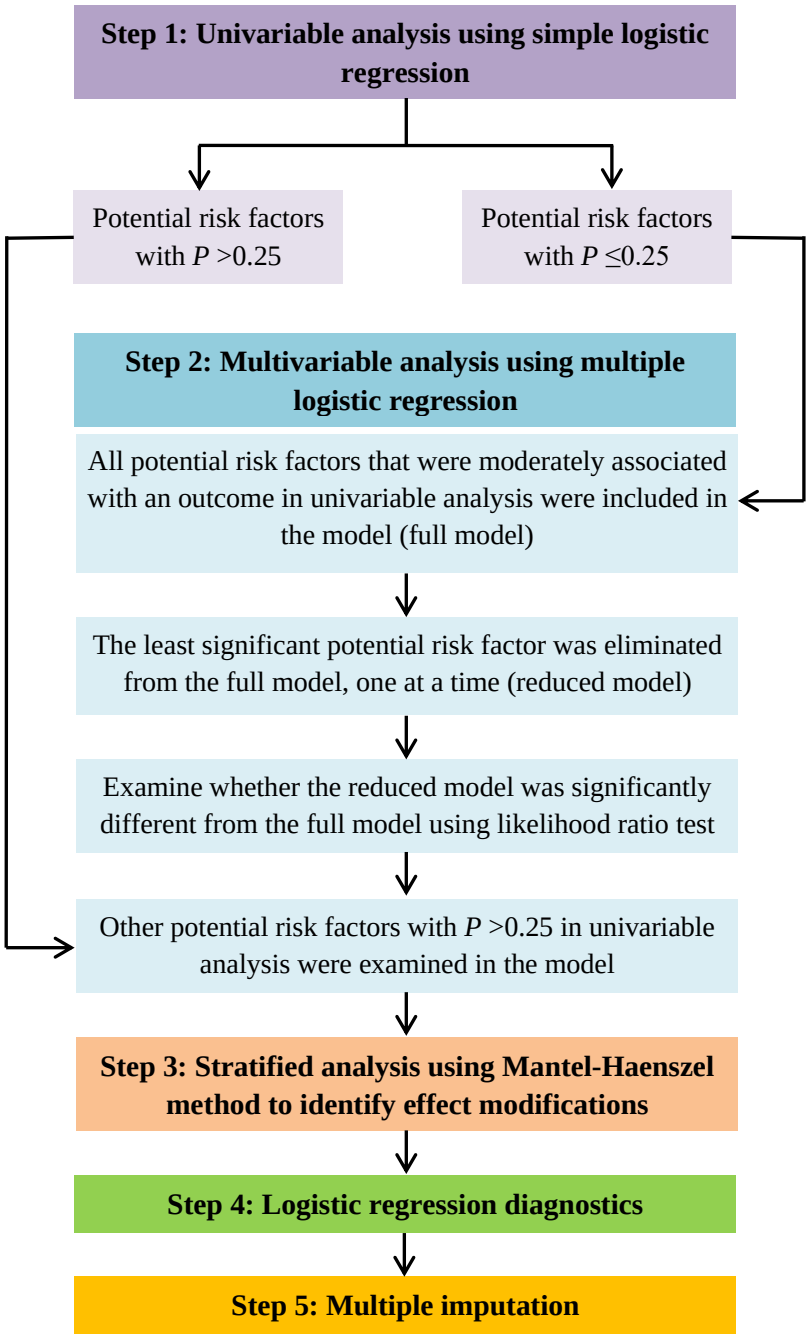


Figure 6.1. Flow diagram of statistical analyses.

6.3.1.2 Multivariable analysis

Risk factors for PTB and SGA were explored using multiple logistic regression (Figure 6.1) by building analysis models specific for each perinatal outcome of interest (PTB and SGA) and group of women (all women, HIV-negative and HIV-positive women). Therefore, a total of six analysis models were built: PTB in all women, HIV-negative and HIV-positive women; SGA in all women, HIV-negative and HIV-positive women. Adjusted OR and 95% CI were reported as effect estimates.

6.3.1.3 Model building

Analysis models were built by performing the following steps (Figure 6.1):

1. All potential risk factors moderately associated ($P \leq 0.25$) with PTB or SGA in the univariable analysis were included in the model – the full model.
2. The least significant potential risk factor was eliminated from the full model, one at a time, and a new model was fitted – the reduced model.
3. The reduced model was compared to the full model using the likelihood ratio test. If the reduced model was significantly different from the full model, the eliminated potential risk factor was retained in the model; otherwise it was removed from the model.
4. The above procedures were performed repeatedly, until a reduced model containing only significant and/or important potential risk factors was obtained.
5. Other potential risk factors with $P > 0.25$ in the univariable analysis were examined in the model by performing the aforementioned steps.

6.3.1.4 Effect modification

Effect modifications between potential risk factors included in the analysis models were explored using the same method as in Chapter 5 – stratified analysis using the Mantel-Haenszel method (Figure 6.1). Significant effect modifications identified from the stratified analysis were tested in the analysis models using the likelihood ratio test, and only those which remained significant were retained in the models.

6.3.1.5 Logistic regression diagnostics

Logistic regression diagnostics including tests for model adequacy and overall goodness of fit were evaluated using "linktest" STATA command and Hosmer and Lemeshow's goodness-of-fit test, respectively.

6.3.1.6 Missing data

Missing data were addressed as in Chapter 5 – multiple imputation by chained equations (MICE). Imputation models were built separately for PTB and SGA.

6.4 Results

6.4.1 Preterm birth

Among the 596 women included in Chapter 5, 18 were excluded due to stillbirth (Figure 5.2). A total of 578 women with live newborns and information on gestational age were included in the present analysis, of whom 364 were HIV-negative and 214 HIV-positive (Figure 6.2). Overall, 99 women had a PTB: 56 HIV-negative and 43 HIV-positive (Figure 6.2).

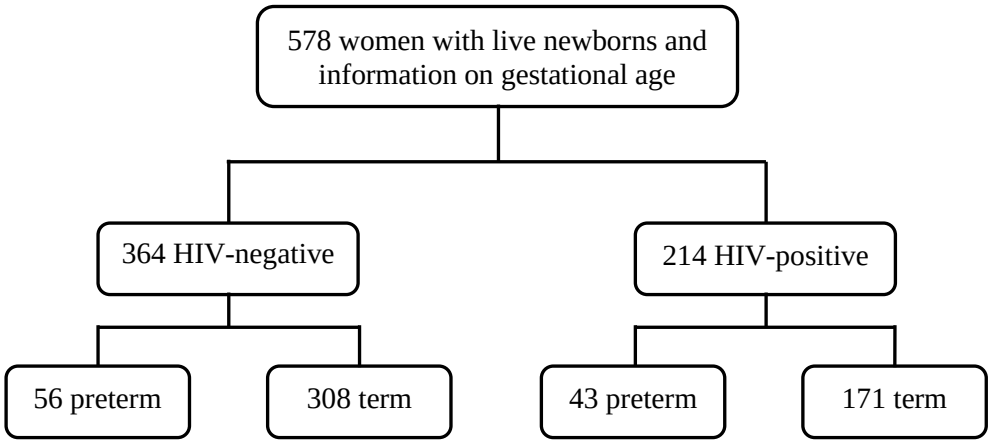


Figure 6.2. Flow diagram of study participants included in the PTB analysis. Abbreviations: HIV, human immunodeficiency virus; PTB, preterm birth.

6.4.1.1 Risk factors for preterm birth in all women

6.4.1.1.1 Univariable analysis

In univariable analysis, treated maternal HIV infection was not associated with PTB (OR: 1.38, 95% CI: 0.89, 2.15) (Table 6.1). However, being nulliparous (OR: 2.05, 95% CI: 1.20, 3.50), experiencing ≥2 previous miscarriages (OR: 2.25, 95% CI: 1.40, 3.63) and inadequate GWG in the third trimester (OR: 2.23, 95% CI: 1.04, 4.77) were associated with an increased risk of PTB (Table 6.1). History of PTB (OR: 1.63, 95% CI: 0.98, 2.72), inadequate GWG in the second trimester (OR: 1.83, 95% CI: 1.00, 3.36) and gestational hypertension (OR: 1.81, 95% CI: 0.94, 3.47) also increased the risk of PTB, but with borderline statistical significance (Table 6.1).

Table 6.1. Univariable analysis of potential risk factors for PTB in all women.

Potential risk factors	Preterm (N=99) n (%)	Term (N=479) n (%)	OR (95% CI)	*P* value[§]
HIV positive	43 (43.4)	171 (35.7)	1.38 (0.89, 2.15)	0.148
Maternal age (years), median (IQR)	31 (27, 36)	31 (26, 36)	1.01 (0.97, 1.05)	0.577
Education (years) median (IQR)	12 (11, 12)	12 (11, 12)	1.02 (0.90, 1.15)	0.795
Single	66 (66.7)	286 (59.7)	1.35 (0.85, 2.13)	0.197
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.3 (22.9, 29.5)	26.7 (23.2, 30.1)	0.97 (0.92, 1.02)	0.286
Nulliparity	24 (24.7)	61 (13.8)	2.05 (1.20, 3.50)	0.008
Number of previous miscarriages ≥2	33 (33.3)	87 (18.2)	2.25 (1.40, 3.63)	0.001
History of preterm birth	26 (26.8)	81 (18.3)	1.63 (0.98, 2.72)	0.060
History of termination of pregnancy	4 (4)	30 (6.3)	0.63 (0.22, 1.83)	0.396
GWG in the second trimester				
Inadequate	46 (46.9)	161 (34.1)	1.83 (1.00, 3.36)	0.051
Adequate	17 (17.4)	109 (23.1)	Reference	–
Excessive	35 (35.7)	202 (42.8)	1.11 (0.59, 2.07)	0.741
GWG in the third trimester				
Inadequate	30 (39.5)	132 (28.6)	2.23 (1.04, 4.77)	0.039
Adequate	10 (13.2)	98 (21.3)	Reference	–
Excessive	36 (47.3)	231 (50.1)	1.53 (0.73, 3.20)	0.262
Gestational hypertension	14 (14.1)	40 (8.4)	1.81 (0.94, 3.47)	0.075
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.2 ± 1.8	12.2 ± 1.6	0.97 (0.85, 1.11)	0.655
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.9 ± 1.7	11.9 ± 1.5	1.00 (0.86, 1.15)	0.967

[§] *P* value from simple logistic regression.
Missing data: <8%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; PTB, preterm birth; SD, standard deviation.

6.4.1.1.2 Multivariable analysis

After adjustment for other covariates in the model (Table 6.2), treated maternal HIV infection was associated with an increased risk of PTB (adjusted OR: 1.56, 95% CI: 0.97, 2.50); however, this association was borderline significant. Nulliparity (adjusted OR: 2.36, 95% CI: 1.25, 4.45), ≥2 previous miscarriages (adjusted OR: 1.89, 95% CI: 1.08, 3.28), history of PTB (adjusted OR: 2.26, 95% CI: 1.30, 3.94), inadequate GWG in the second trimester (adjusted OR: 1.90, 95% CI: 1.01, 3.58) and gestational hypertension (adjusted OR: 1.89, 95% CI: 0.95,

3.76) were associated with an increased risk of PTB (Table 6.2). For gestational hypertension, however, the association was borderline significant (Table 6.2).

Table 6.2. Multivariable analysis of risk factors for PTB in all women.

Risk factors	Adjusted OR (95% CI)[§]
HIV positive	1.56 (0.97, 2.50)
Nulliparity	2.36 (1.25, 4.45)
Number of previous miscarriages ≥2	1.89 (1.08, 3.28)
History of preterm birth	2.26 (1.30, 3.94)
Inadequate GWG in the second trimester	1.90 (1.01, 3.58)
Gestational hypertension	1.89 (0.95, 3.76)

[§] Adjusted for all variables in the table.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.1.3 Effect modification

In stratified analysis, there was a significant effect modification between maternal HIV and marital status, and this remained significant after adjustment for other covariates in the final model (Table 6.3). The effect of treated maternal HIV infection on PTB risk differed by marital status: among single women (adjusted OR: 2.08, 95% CI: 1.16, 3.73), but not among married/cohabiting women (adjusted OR: 0.75, 95% CI: 0.31, 1.82), treated maternal HIV infection was associated with a higher risk of PTB (Table 6.4). Similarly, the effect of being single on PTB risk differed by maternal HIV status: among HIV-positive women (adjusted OR: 2.70, 95% CI: 1.15, 6.38), but not among HIV-negative women (adjusted OR: 0.97, 95% CI: 0.52, 1.80), being single was associated with a higher risk of PTB (Table 6.4). The inclusion of this effect modification in the final model resulted in slight changes in the magnitude of effect estimates of nulliparity, number of previous miscarriages, history of PTB, inadequate GWG in

the second trimester, and gestational hypertension; however, the interpretation of their effect estimates remained the same (Table 6.2 and Table 6.3).

Table 6.3. Multivariable analysis of risk factors for PTB in all women with an effect modification between maternal HIV and marital status.

Risk factors	Adjusted OR (95% CI)[§]
HIV positive[I]	0.75 (0.31, 1.82)
Single[I]	0.97 (0.52, 1.80)
Effect modification: HIV-positive and single[I]	2.79 (1.04, 8.01)
Nulliparity	2.33 (1.22, 4.44)
Number of previous miscarriages ≥2	1.96 (1.12, 3.44)
History of preterm birth	2.27 (1.30, 3.97)
Inadequate GWG in the second trimester	1.90 (1.01, 3.60)
Gestational hypertension	1.85 (0.92, 3.69)

[§] Adjusted for all variables in the table.
[I] See Table 6.4.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Table 6.4. Effect modification between maternal HIV and marital status on the risk of PTB in all women.

	Adjusted OR (95% CI)[§]			
	Marital status		Maternal HIV status	
	Single	Married	HIV-negative	HIV-positive
HIV positive	2.08 (1.16, 3.73)	0.75 (0.31, 1.82)		
Single			0.97 (0.52, 1.80)	2.70 (1.15, 6.38)

[§] Adjusted for all variables in Table 6.3.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.1.4 Logistic regression diagnostics

The "linktest" STATA command showed that the final model (Table 6.3) was specified correctly, i.e. no specification error, with *P* values 0.026 and 0.914 for _hat and _hatsq, respectively. The Hosmer and Lemeshow goodness-of-fit test indicated that the final model (Table 6.3) fitted the data well (*P* value 0.571).

6.4.1.1.5 Multiple imputation

The rate of missing data in the final model (Table 6.3) was 8%. Variables with missing data were parity (6.8%), history of PTB (6.8%) and GWG in the second trimester (1.4%). Missingness in the present analysis was considered as missing at random. All variables in the final model (Table 6.3) were included in the imputation model. Effect modification between maternal HIV and marital status was passively imputed as a statistical interaction. Several auxiliary variables were added to the imputation model, including maternal age, education, SES, pre-pregnancy body mass index (BMI), GWG in the third trimester and history of LBW. Twenty imputations were performed [489]. The results of multivariable analysis in multiple imputation were comparable with those in complete-case analysis (Table 6.5), including for the effect modification between maternal HIV and marital status (Table 6.6 and Table 6.7).

Table 6.5. Multivariable analysis of risk factors for PTB in all women based on complete-case versus multiple imputation.

Risk factors	Adjusted OR (95% CI)[§]	
	Complete-case	Multiple imputation
HIV positive[I]	0.75 (0.31, 1.82)	0.73 (0.30, 1.77)
Single[I]	0.97 (0.52, 1.80)	0.90 (0.49, 1.65)
Effect modification: HIV-positive and single[I]	2.79 (1.04, 8.01)	2.88 (1.03, 7.20)
Nulliparity	2.33 (1.22, 4.44)	2.14 (1.12, 4.06)
Number of previous miscarriages ≥2	1.96 (1.12, 3.44)	2.15 (1.23, 3.51)
History of preterm birth	2.27 (1.30, 3.97)	2.17 (1.23, 3.81)
Inadequate GWG in the second trimester	1.90 (1.01, 3.60)	2.04 (1.09, 3.61)
Gestational hypertension	1.85 (0.92, 3.69)	1.80 (0.91, 3.58)

[§] Adjusted for all variables in the table.
[I] See Table 6.6 and Table 6.7.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Table 6.6. Effect of treated maternal HIV infection on PTB risk within strata of marital status, based on complete-case versus multiple imputation.

	Adjusted OR (95% CI)[§]			
	Complete-case		Multiple imputation	
	Single	Married	Single	Married
HIV positive	2.08 (1.16, 3.73)	0.75 (0.31, 1.82)	2.10 (1.19, 3.72)	0.73 (0.30, 1.77)

[§] Adjusted for all variables in Table 6.5.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Table 6.7. Effect of being single on PTB risk within strata of maternal HIV status, based on complete-case versus multiple imputation.

	Adjusted OR (95% CI)[§]			
	Complete-case		Multiple imputation	
	HIV-negative	HIV-positive	HIV-negative	HIV-positive
Single	0.97 (0.52, 1.80)	2.70 (1.15, 6.38)	0.90 (0.49, 1.65)	2.60 (1.11, 6.11)

[§] Adjusted for all variables in Table 6.5.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.2 Risk factors for preterm birth in HIV-negative women

6.4.1.2.1 Univariable analysis

In univariable analysis, nulliparity (OR: 2.62, 95% CI: 1.37, 5.02) and ≥2 previous miscarriages (OR: 3.85, 95% CI: 2.12, 6.98) were associated with an increased risk of PTB (Table 6.8).

6.4.1.2.2 Multivariable analysis

In multivariable analysis, nulliparity (adjusted OR: 2.13, 95% CI: 0.96, 4.72), ≥2 previous miscarriages (adjusted OR: 3.10, 95% CI: 1.55, 6.22) and history of PTB (adjusted OR: 2.17, 95% CI: 1.00, 4.70) were associated with an increased risk of PTB. However, only ≥2 previous miscarriages was statistically significant (Table 6.9).

Table 6.8. Univariable analysis of potential risk factors for PTB in HIV-negative women.

Potential risk factors	Preterm (N=56) n (%)	Term (N=308) n (%)	OR (95% CI)	*P* value[§]
Maternal age (years), median (IQR)	28 (26, 34)	30 (25, 34)	1.01 (0.96, 1.06)	0.574
Education (years) median (IQR)	12 (12, 12)	12 (12, 12)	1.10 (0.92, 1.31)	0.287
Single	31 (55.4)	178 (57.8)	0.90 (0.51, 1.61)	0.735
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.9 (24.1, 29.8)	26.7 (23.4, 30.3)	0.99 (0.92, 1.06)	0.745
Nulliparity	18 (33.3)	45 (16)	2.62 (1.37, 5.02)	0.004
Number of previous miscarriages ≥2	27 (48.2)	60 (19.5)	3.85 (2.12, 6.98)	<0.001
History of preterm birth	13 (24.1)	53 (18.9)	1.36 (0.68, 2.72)	0.379
History of termination of pregnancy	2 (3.6)	16 (5.2)	0.67 (0.15, 3.02)	0.608
GWG in the second trimester				
Inadequate	21 (38.2)	97 (32)	1.56 (0.67, 3.63)	0.298
Adequate	9 (16.4)	65 (21.5)	Reference	–
Excessive	25 (45.4)	141 (46.5)	1.28 (0.57, 2.90)	0.553
GWG in the third trimester				
Inadequate	13 (28.9)	79 (26.5)	1.19 (0.46, 3.07)	0.714
Adequate	8 (17.8)	58 (19.5)	Reference	–
Excessive	24 (53.3)	161 (54)	1.08 (0.46, 2.54)	0.859
Gestational hypertension	8 (14.3)	26 (8.4)	1.81 (0.77, 4.23)	0.172
Haemoglobin level in the first trimester (g/dL), mean ± SD	12 ± 2	12.3 ± 1.7	0.90 (0.77, 1.07)	0.234
Haemoglobin level in the second trimester (g/dL), mean ± SD	12.2 ± 1.7	12 ± 1.5	1.07 (0.88, 1.29)	0.506

[§] *P* value from simple logistic regression.
Missing data: <6%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; PTB, preterm birth; SD, standard deviation.

Table 6.9. Multivariable analysis of risk factors for PTB in HIV-negative women.

Risk factors	Adjusted OR (95% CI)[§]
Nulliparity	2.13 (0.96, 4.72)
Number of previous miscarriages ≥2	3.10 (1.55, 6.22)
History of preterm birth	2.17 (1.00, 4.70)

[§] Adjusted for all variables in the table and GWG in the second trimester.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.2.3 Effect modification

No effect modifications were identified in the stratified analysis.

6.4.1.2.4 Logistic regression diagnostics

The final model (Table 6.9) was specified correctly with *P* values 0.042 and 0.863 for _hat and _hatsq, respectively. The final model (Table 6.9) also fitted the data well, as indicated by the *P* value of 0.389 in Hosmer and Lemeshow's goodness-of-fit test.

6.4.1.2.5 Multiple imputation

The rate of incomplete cases in the final model (Table 6.9) was 9.3%. Variables with incomplete cases were parity (8%), history of PTB (8%) and GWG in the second trimester (1.7%). The imputation model generated in the analysis of PTB in all women was used. Table 6.10 shows comparable results for multivariable analysis in multiple imputation to those in the complete-case analysis.

Table 6.10. Multivariable analysis of risk factors for PTB in HIV-negative women based on complete-case versus multiple imputation.

Risk factors	**Adjusted OR (95% CI)[§]**	
	Complete-case	**Multiple imputation**
Nulliparity	2.13 (0.96, 4.72)	2.02 (0.92, 4.42)
Number of previous miscarriages ≥2	3.10 (1.55, 6.22)	3.34 (1.69, 6.26)
History of preterm birth	2.17 (1.00, 4.70)	2.10 (0.98, 4.51)

[§] Adjusted for all variables in the table and GWG in the second trimester.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.3 Risk factors for preterm birth in HIV-positive women

6.4.1.3.1 Univariable analysis

The univariable analysis showed an increased risk of PTB in HIV-positive women who were single (OR: 2.55, 95% CI: 1.11, 5.84), had a history of PTB (OR: 2.06, 95% CI: 0.95, 4.44) and inadequate GWG in the third trimester (OR: 6.42, 95%

CI: 1.40, 29.38) (Table 6.11). For history of PTB, however, the association was borderline significant (Table 6.11).

Table 6.11. Univariable analysis of potential risk factors for PTB in HIV-positive women.

Potential risk factors	Preterm (N=43) n (%)	Term (N=171) n (%)	OR (95% CI)	*P* value[§]
Maternal age (years), median (IQR)	31 (28, 38)	33 (28, 37)	0.99 (0.94, 1.05)	0.857
Education (years) median (IQR)	12 (11, 12)	12 (11, 12)	0.95 (0.80, 1.13)	0.580
Single	35 (81.4)	108 (63.2)	2.55 (1.11, 5.84)	0.027
Pre-pregnancy BMI (kg/m^2), median (IQR)	25.6 (22.5, 28.8)	26.4 (23, 30)	0.95 (0.88, 1.03)	0.236
Nulliparity	6 (14)	16 (9.9)	1.47 (0.54, 4.02)	0.453
Number of previous miscarriages ≥2	6 (13.9)	27 (15.8)	0.86 (0.33, 2.25)	0.766
History of preterm birth	13 (30.2)	28 (17.4)	2.06 (0.95, 4.44)	0.065
History of termination of pregnancy	2 (4.6)	14 (8.2)	0.55 (0.12, 2.50)	0.437
GWG in the second trimester				
Inadequate	25 (58.1)	64 (37.9)	2.15 (0.89, 5.20)	0.090
Adequate	8 (18.6)	44 (26)	Reference	–
Excessive	10 (23.3)	61 (36.1)	0.90 (0.33, 2.47)	0.840
GWG in the third trimester				
Inadequate	17 (54.8)	53 (32.5)	6.42 (1.40, 29.38)	0.017
Adequate	2 (6.5)	40 (24.5)	Reference	–
Excessive	12 (38.7)	70 (43)	3.43 (0.73, 16.10)	0.118
Gestational hypertension	6 (14)	14 (8.2)	1.82 (0.65, 5.05)	0.251
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.3 ± 1.3	12.1 ± 1.6	1.11 (0.88, 1.39)	0.364
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.6 ± 1.7	11.8 ± 1.4	0.92 (0.73, 1.16)	0.506

[§] *P* value from simple logistic regression.
Missing data: <10%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; PTB, preterm birth; SD, standard deviation.

6.4.1.3.2 Multivariable analysis

After adjustment for other covariates in the final model (Table 6.12), inadequate GWG in the third trimester remained associated with an increased risk of PTB (adjusted OR: 4.58, 95% CI: 1.02, 21.95). In addition, the odds of PTB decreased by 12% for each additional $1kg/m^2$ of pre-pregnancy BMI (adjusted OR: 0.88, 95% CI: 0.79, 0.98) (Table 6.12).

Table 6.12. Multivariable analysis of risk factors for PTB in HIV-positive women.

Risk factors	Adjusted OR (95% CI)[§]
Pre-pregnancy BMI	0.88 (0.79, 0.98)
Inadequate GWG in the second trimester	2.28 (0.80, 6.48)
Inadequate GWG in the third trimester	4.58 (1.02, 21.95)

[§] Adjusted for all variables in the table and history of PTB.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.1.3.3 Effect modification

No effect modifications were identified in stratified analysis.

6.4.1.3.4 Logistic regression diagnostics

The "linktest" STATA command showed *P* values 0.018 and 0.379 for _hat and _hatsq, respectively – suggesting that there was no specification error in the final model (Table 6.12). The Hosmer and Lemeshow goodness-of-fit test showed a *P* value of 0.425 – suggesting the final model (Table 6.12) fitted the data well.

6.4.1.3.5 Multiple imputation

The rate of missing data in the final model (Table 6.12) was 14%. Variables with missing data were history of PTB (4.7%) and GWG in the second (0.9%) and third trimester (9.4%). The imputation model generated in the analysis of PTB in all women was used. Overall, the interpretation of the results of multivariable analysis in multiple imputation were similar to those in complete-case analysis (Table 6.13).

Table 6.13. Multivariable analysis of risk factors for PTB in HIV-positive women based on complete-case versus multiple imputation.

Risk factors	Adjusted OR (95% CI)[§]	
	Complete-case	Multiple imputation
Pre-pregnancy BMI	0.88 (0.79, 0.98)	0.92 (0.83, 0.97)
Inadequate GWG in the second trimester	2.28 (0.80, 6.48)	2.46 (0.83, 6.47)
Inadequate GWG in the third trimester	4.58 (1.02, 21.95)	4.81 (1.10, 21.83)

[§] Adjusted for all variables in the table and history of PTB.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

6.4.2 Small for gestational age

Among the 578 women included in the PTB analysis (Figure 6.2), 10 were excluded due to missing information on birth weight (n=8) and gestational age at birth outside the range of 24–42 weeks (n=2) (Figure 6.3). The risk factors analysis of SGA included 568 women: 359 HIV-negative and 209 HIV-positive (Figure 6.3). Overall, 106 babies were born SGA: 58 to HIV-negative and 48 to HIV-positive women (Figure 6.3).

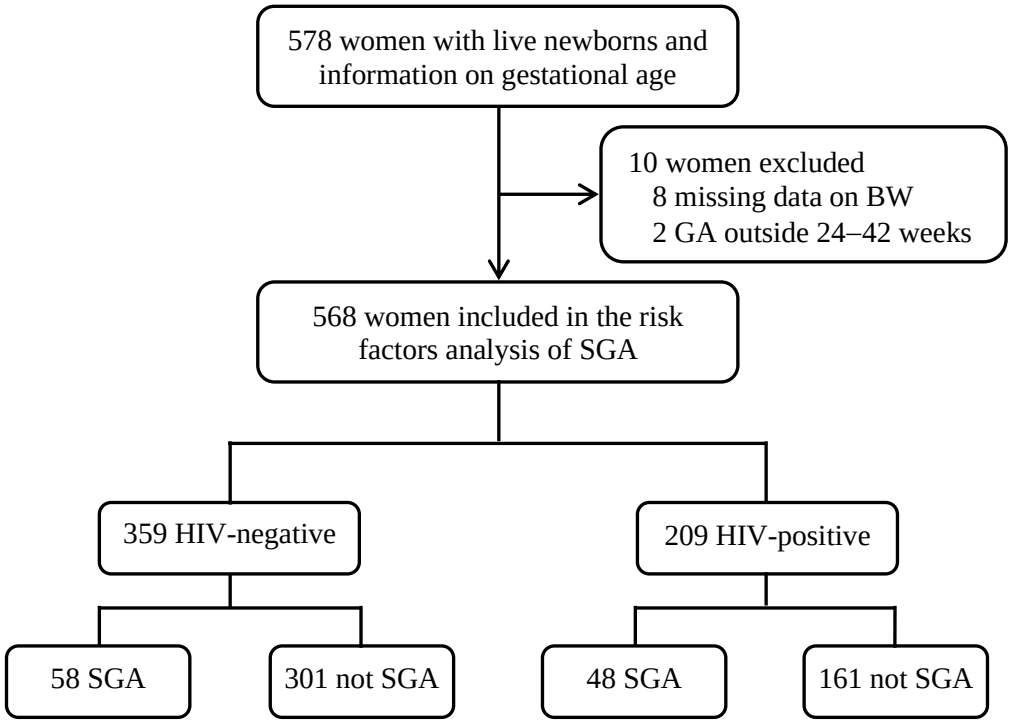


Figure 6.3. Flow diagram of study participants included in the SGA analysis. Abbreviations: BW, birth weight; GA, gestational age; HIV, human immunodeficiency virus; SGA, small for gestational age.

6.4.2.1 Risk factors for small for gestational age in all women

6.4.2.1.1 Univariable analysis

The univariable analysis showed that treated maternal HIV infection (OR: 1.55, 95% CI: 1.01, 2.37), history of termination of pregnancy (OR: 2.55, 95% CI: 1.22, 5.34), inadequate GWG in the third trimester (OR: 2.55, 95% CI: 1.39, 4.65) and gestational hypertension (OR: 1.79, 95% CI: 0.94, 3.38) were associated with an increased risk of SGA (Table 6.14). However, for gestational hypertension, the association was borderline significant (Table 6.14). Maternal education (OR: 0.91, 95% CI: 0.81, 1.02), pre-pregnancy BMI (OR: 0.95, 95% CI: 0.90, 0.99), excessive GWG in the third trimester (OR: 0.57, 95% CI: 0.30, 1.09) and haemoglobin level in the second trimester (OR: 0.86, 95% CI: 0.75, 0.99) were associated with a decreased risk of SGA (Table 6.14). However, for education and excessive GWG in the third trimester, the associations were borderline significant (Table 6.14).

6.4.2.1.2 Multivariable analysis

After controlling for other covariates in the final model (Table 6.15), treated maternal HIV infection remained associated with a higher risk of SGA (adjusted OR: 1.55, 95% CI: 0.98, 2.52); however, this association became borderline significant. History of termination of pregnancy (adjusted OR: 2.73, 95% CI: 1.19, 6.27) and inadequate GWG in the third trimester (adjusted OR: 2.60, 95% CI: 1.37, 4.95) were consistently associated with a higher risk of SGA (Table 6.15). Nulliparity became associated with a higher risk of SGA (adjusted OR: 1.85, 95% CI: 0.98, 3.48), but with borderline statistical significance (Table 6.15).

The association between pre-pregnancy BMI and a lower risk of SGA persisted in this adjusted analysis (adjusted OR: 0.92, 95% CI: 0.89, 0.99) (Table 6.15).

Table 6.14. Univariable analysis of potential risk factors for SGA in all women.

Potential risk factors	SGA (N=106) n (%)	Not SGA (N=462) n (%)	OR (95% CI)	*P* value[§]
HIV positive	48 (45.3)	161 (34.8)	1.55 (1.01, 2.37)	0.045
Maternal age (years), median (IQR)	32 (27, 37)	31 (26, 35)	1.02 (0.99, 1.06)	0.230
Education (years), median (IQR)	12 (11, 12)	12 (11, 12)	0.91 (0.81, 1.02)	0.098
Single	69 (65.1)	276 (59.7)	1.26 (0.81, 1.95)	0.309
Pre-pregnancy BMI (kg/m^2), median (IQR)	25.5 (22.4, 29.7)	26.9 (23.4, 30)	0.95 (0.90, 0.99)	0.047
Nulliparity	20 (20.4)	64 (14.9)	1.47 (0.84, 2.57)	0.176
Number of previous miscarriages ≥2	23 (21.7)	95 (20.6)	1.07 (0.64, 1.79)	0.795
History of preterm birth	22 (22.4)	82 (19)	1.23 (0.72, 2.10)	0.442
History of termination of pregnancy	12 (11.3)	22 (4.8)	2.55 (1.22, 5.34)	0.013
GWG in the second trimester				
Inadequate	50 (47.6)	152 (33.4)	1.07 (0.63, 1.80)	0.811
Adequate	29 (27.6)	94 (20.7)	Reference	–
Excessive	26 (24.8)	209 (45.9)	1.03 (0.77, 1.13)	0.273
GWG in the third trimester				
Inadequate	54 (54.5)	106 (24.6)	2.55 (1.39, 4.65)	0.002
Adequate	18 (18.2)	90 (20.9)	Reference	–
Excessive	27 (27.3)	235 (54.5)	0.57 (0.30, 1.09)	0.092
Gestational hypertension	15 (14.2)	39 (8.4)	1.79 (0.94, 3.38)	0.074
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.3 ± 1.6	12.2 ± 1.8	1.04 (0.91, 1.18)	0.567
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.7 ± 1.5	12 ± 1.5	0.86 (0.75, 0.99)	0.037

[§] *P* value from simple logistic regression.
Missing data: <7%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

Table 6.15. Multivariable analysis of risk factors for SGA in all women.

Risk factors	Adjusted OR (95% CI)[§]
HIV positive	1.55 (0.98, 2.52)
Pre-pregnancy BMI	0.92 (0.89, 0.99)
Nulliparity	1.85 (0.98, 3.48)
History of termination of pregnancy	2.73 (1.19, 6.27)
Inadequate GWG in the third trimester	2.60 (1.37, 4.95)
Gestational hypertension	1.90 (0.87, 4.14)

[§] Adjusted for all variables in the table.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.4.2.1.3 Effect modification

No effect modifications were identified in stratified analysis.

6.4.2.1.4 Logistic regression diagnostics

The results of "linktest" STATA command showed that the final model (Table 6.15) was specified correctly with *P* values 0.002 and 0.562 for _hat and _hatsq, respectively. The final model (Table 6.15) also fitted the data well, as shown by a *P* value of 0.359 in Hosmer and Lemeshow's goodness-of-fit test.

6.4.2.1.5 Multiple imputation

The rate of missing data in the final model (Table 6.15) was 13.2%. Missing data were observed in parity (6.9%) and GWG in the third trimester (6.7%). Missingness in the present analysis was assumed as missing at random. The imputation model included all variables in the final model (Table 6.15) and several auxiliary variables, including maternal age, marital status, number of previous miscarriages, histories of PTB and LBW, and GWG in the second trimester. Twenty imputations were performed after considering the 13.2% of missing data in the final model [489].

The association between treated maternal HIV-infection and an increased risk of SGA, which was borderline significant in the complete-case analysis (adjusted OR: 1.55, 95% CI: 0.98, 2.52), became statistically significant in multiple imputation (adjusted OR: 1.59, 95% CI: 1.06, 2.33) (Table 6.16). For other risk factors, the multiple imputation and complete-case analysis produced similar results (Table 6.16).

Table 6.16. Multivariable analysis of risk factors for SGA in all women based on complete-case versus multiple imputation.

Risk factors	Adjusted OR (95% CI)[§]	
	Complete-case	Multiple imputation
HIV positive	1.55 (0.98, 2.52)	1.59 (1.06, 2.33)
Pre-pregnancy BMI	0.92 (0.89, 0.99)	0.93 (0.88, 0.98)
Nulliparity	1.85 (0.98, 3.48)	1.77 (0.95, 3.29)
History of termination of pregnancy	2.73 (1.19, 6.27)	2.63 (1.15, 5.99)
Inadequate GWG in the third trimester	2.60 (1.37, 4.95)	2.75 (1.48, 5.03)
Gestational hypertension	1.90 (0.87, 4.14)	1.85 (0.87, 3.92)

[§] Adjusted for all variables in the table.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.4.2.2 Risk factors for small for gestational age in HIV-negative women

6.4.2.2.1 Univariable analysis

The unadjusted analysis showed that excessive GWG in the third trimester (OR: 0.47, 95% CI: 0.21, 1.04) and haemoglobin level in the second trimester (OR: 0.79, 95% CI: 0.66, 0.96) were associated with a lower risk of SGA; however, the former was borderline significant (Table 6.17).

6.4.2.2.2 Multivariable analysis

After controlling for other covariates in the final model (Table 6.18), haemoglobin level in the second trimester remained associated with a lower risk of SGA (adjusted OR: 0.78, 95% CI: 0.63, 0.98). Conversely, having ≥2 previous miscarriages was associated with a higher risk of SGA (adjusted OR: 2.24, 95% CI: 1.09, 4.61) (Table 6.18).

6.4.2.2.3 Effect modification

No effect modifications were identified in stratified analysis.

Table 6.17. Univariable analysis of potential risk factors for SGA in HIV-negative women.

Potential risk factors	SGA (N=58) n (%)	Not SGA (N=301) n (%)	OR (95% CI)	*P* value[§]
Maternal age (years), median (IQR)	29.5 (25, 33)	30 (26, 34)	0.99 (0.94, 1.04)	0.752
Education (years), median (IQR)	12 (12, 12)	12 (12, 12)	0.92 (0.79, 1.07)	0.280
Single	39 (67.2)	168 (55.8)	1.62 (0.90, 2.94)	0.109
Pre-pregnancy BMI (kg/m^2), median (IQR)	25.5 (23.8, 29.7)	26.9 (23.6, 30.4)	0.96 (0.90, 1.02)	0.221
Nulliparity	13 (25)	49 (17.6)	1.56 (0.77, 3.13)	0.214
Number of previous miscarriages ≥2	17 (29.3)	68 (22.6)	1.42 (0.76, 2.66)	0.272
History of preterm birth	12 (23.1)	53 (19.1)	1.27 (0.62, 2.59)	0.505
History of termination of pregnancy	4 (6.9)	14 (4.7)	1.52 (0.48, 4.79)	0.476
GWG in the second trimester				
Inadequate	29 (50.9)	88 (29.7)	1.65 (0.78, 3.48)	0.191
Adequate	12 (21)	60 (20.3)	Reference	–
Excessive	16 (28.1)	148 (50)	0.54 (0.24, 1.21)	0.135
GWG in the third trimester				
Inadequate	25 (46.3)	66 (23.2)	1.70 (0.78, 3.71)	0.178
Adequate	12 (22.2)	54 (19)	Reference	–
Excessive	17 (31.5)	164 (57.8)	0.47 (0.21, 1.04)	0.062
Gestational hypertension	8 (13.8)	26 (8.6)	1.69 (0.72, 3.95)	0.224
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.6 ± 1.5	12.2 ± 1.9	1.13 (0.96, 1.33)	0.149
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.6 ± 1.5	12.1 ± 1.6	0.79 (0.66, 0.96)	0.016

[§] *P* value from simple logistic regression.
Missing data: <6%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

Table 6.18. Multivariable analysis of risk factors for SGA in HIV-negative women.

Risk factors	Adjusted OR (95% CI)[§]
Single	1.74 (0.88, 3.43)
Number of previous miscarriages ≥2	2.24 (1.09, 4.61)
Haemoglobin level in the second trimester	0.78 (0.63, 0.98)

[§] Adjusted for all variables in the table, GWG in the second and third trimesters and haemoglobin level in the first trimester.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.4.2.2.4 Logistic regression diagnostics

The "linktest" STATA command showed that the final model (Table 6.18) was specified correctly with *P* values 0.041 and 0.336 for _hat and _hatsq, respectively. The Hosmer and Lemeshow goodness-of-fit test showed that the final model (Table 6.18) fitted the data well (*P*=0.376).

6.4.2.2.5 Multiple imputation

The rate of missing data in the final model (Table 6.18) was 10.9%. Variables with missing data were GWG in the second (1.7%) and third trimesters (5.9%), and haemoglobin levels in the first (4.2%) and second trimesters (2.8%). The imputation model generated in the analysis of SGA in all women was used. Table 6.19 shows that the results in multiple imputation were comparable to those in the complete-case analysis.

Table 6.19. Multivariable analysis of risk factors for SGA in HIV-negative women based on complete-case versus multiple imputation.

Risk factors	Adjusted OR (95% CI)[§]	
	Complete-case	Multiple imputation
Single	1.74 (0.88, 3.43)	1.78 (0.96, 3.38)
Number of previous miscarriages ≥2	2.24 (1.09, 4.61)	2.19 (1.10, 4.59)
Haemoglobin level in the second trimester	0.78 (0.63, 0.98)	0.78 (0.63, 0.96)

[§] Adjusted for all variables in the table, GWG in the second and third trimesters and haemoglobin level in the first trimester.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.4.2.3 Risk factors for small for gestational age in HIV-positive women

6.4.2.3.1 Univariable analysis

In univariable analysis, maternal age (OR: 1.05, 95% CI: 0.99, 1.11), history of termination of pregnancy (OR: 3.82, 95% CI: 1.35, 10.82) and inadequate GWG in the third trimester (OR: 4.35, 95% CI: 1.62, 11.68) were associated with an

increased risk of SGA (Table 6.20). For maternal age, however, the association was borderline significant (Table 6.20). Pre-pregnancy BMI (OR: 0.94, 95% CI: 0.87, 1.02) and excessive GWG in the second trimester (OR: 0.33, 95% CI: 0.14, 0.80) were associated with a decreased risk of SGA; however, the former was borderline significant (Table 6.20).

Table 6.20. Univariable analysis of potential risk factors for SGA in HIV-positive women.

Potential risk factors	**SGA (N=48) n (%)**	**Not SGA (N=161) n (%)**	**OR (95% CI)**	***P* value[§]**
Maternal age (years), median (IQR)	34 (29.5, 38)	32 (28, 37)	1.05 (0.99, 1.11)	0.090
Education (years), median (IQR)	12 (11, 12)	12 (11, 12)	0.92 (0.78, 1.09)	0.333
Single	30 (62.5)	108 (67.1)	0.82 (0.42, 1.60)	0.557
Pre-pregnancy BMI (kg/m^2), median (IQR)	25.4 (21.7, 29.3)	26.7 (23.4, 30)	0.94 (0.87, 1.02)	0.129
Nulliparity	7 (15.2)	15 (9.8)	1.65 (0.63, 4.33)	0.308
Number of previous miscarriages ≥2	6 (12.5)	27 (16.8)	0.71 (0.27, 1.83)	0.478
History of preterm birth	10 (21.7)	29 (18.9)	1.19 (0.53, 2.67)	0.677
History of termination of pregnancy	8 (16.7)	8 (5)	3.82 (1.35, 10.82)	0.011
GWG in the second trimester				
Inadequate	21 (43.8)	64 (40.2)	0.66 (0.31, 1.41)	0.279
Adequate	17 (35.4)	34 (21.4)	Reference	–
Excessive	10 (20.8)	61 (38.4)	0.33 (0.14, 0.80)	0.014
GWG in the third trimester				
Inadequate	29 (64.5)	40 (27.2)	4.35 (1.62, 11.68)	0.004
Adequate	6 (13.3)	36 (24.5)	Reference	–
Excessive	10 (22.2)	71 (48.3)	0.85 (0.28, 2.51)	0.762
Gestational hypertension	7 (14.6)	13 (8.1)	1.94 (0.73, 5.19)	0.185
Haemoglobin level in the first trimester (g/dL), mean ± SD	12 ± 1.7	12.2 ± 1.5	0.91 (0.74, 1.12)	0.385
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.7 ± 1.5	11.8 ± 1.5	0.99 (0.79, 1.23)	0.919

[§] *P* value from simple logistic regression.
Missing data: <9%.
Abbreviations: BMI, body mass index; CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; SD, standard deviation; SGA, small for gestational age.

6.4.2.3.2 Multivariable analysis

In the adjusted analysis, history of termination of pregnancy (adjusted OR: 3.39, 95% CI: 1.06, 10.83) and inadequate GWG in the third trimester (adjusted OR:

4.89, 95% CI: 1.74, 13.77) remained associated with an increased risk of SGA (Table 6.21). However, the association between excessive GWG in the second trimester and a decreased risk of SGA became borderline significant (adjusted OR: 0.39, 95% CI: 0.15, 1.09) (Table 6.21).

Table 6.21. Multivariable analysis of risk factors for SGA in HIV-positive women.

Risk factors	Adjusted OR (95% CI)[§]
History of termination of pregnancy	3.39 (1.06, 10.83)
Excessive GWG in the second trimester	0.39 (0.15, 1.09)
Inadequate GWG in the third trimester	4.89 (1.74, 13.77)

[§] Adjusted for all variables in the table and maternal age.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.4.2.3.3 Effect modification

No effect modifications were identified in stratified analysis.

6.4.2.3.4 Logistic regression diagnostics

The *P* values of "linktest" STATA command were 0.042 and 0.448 for _hat and _hatsq, respectively – indicating that the final model (Table 6.21) was specified correctly. Hosmer and Lemeshow's goodness-of-fit test gave a *P* value of 0.537 – suggesting that the final model (Table 6.21) fitted the data well.

6.4.2.3.5 Multiple imputation

The rate of incomplete cases in the final model (Table 6.21) was 8.1%. Variables with incomplete cases were GWG in the second (1.0%) and third trimesters (8.1%). The imputation model generated in the analysis of SGA in all women was used. Table 6.22 shows that the results of multivariable analysis in multiple imputation were similar to those in the complete-case analysis.

Table 6.22. Multivariable analysis of risk factors for SGA in HIV-positive women based on complete-case versus multiple imputation.

Risk factors	Adjusted OR (95% CI)[§]	
	Complete-case	**Multiple imputation**
History of termination of pregnancy	3.39 (1.06, 10.83)	3.35 (1.08, 10.66)
Excessive GWG in the second trimester	0.39 (0.15, 1.09)	0.40 (0.27, 1.11)
Inadequate GWG in the third trimester	4.89 (1.74, 13.77)	4.74 (1.76, 13.61)

[§] Adjusted for all variables in the table and maternal age.
Abbreviations: CI, confidence interval; GWG, gestational weight gain; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

6.5 Discussion

6.5.1 Risk factors for preterm birth

In the analysis of all women, the association between treated maternal HIV infection and an increased risk of PTB was borderline significant. However, when the analysis was stratified by marital status, the association became significant, i.e. treated maternal HIV infection was a risk factor for PTB in single women, but not in married/cohabiting women. Being single was also a risk factor for PTB in HIV-positive women, but not in HIV negative women. Other risk factors for PTB in all women included nulliparity, ≥2 previous miscarriages, history of PTB, inadequate GWG in the second trimester and gestational hypertension.

The borderline significant association between treated maternal HIV infection and PTB in this chapter is somewhat different from the meta-analysis in Chapter 3 (Figure 3.2), which showed a significant association. The meta-analysis included 15 studies (153,905 women): eight were conducted in Africa [14,15,28,29,96,356,394,402], four in Europe [406,410,411,417] and three in the Americas [422,423,425] (Chapter 3: Figure 3.2). However, the majority, especially African studies, did not use first-trimester ultrasound to estimate gestational age (Chapter 3 – Appendix 3.6: Table 3.1). Insufficient statistical power [473,474], as evidenced by the relatively wide CI (Table 6.2), may partly explain why the association between treated maternal HIV infection and PTB in the present study did not reach statistical significance. Table 6.23 shows the power calculations for a future study with the same study characteristics and sample size as the present study: 578 women (364 HIV-negative and 214 HIV-

positive). P_1 and P_2 (Table 6.23) indicate the proportions of PTB in HIV-negative and HIV-positive women, respectively. The proportion of PTB in HIV-negative women in the present study was 15.4% (Figure 6.2). Table 6.23 shows that, in a future study, if the proportion of PTB in HIV-negative women (P_1) was 15%, statistical power of 85% would be detected if the proportion of PTB in HIV-positive women (P_2) was 25%.

Table 6.23. Hypothetical scenario of power calculations for future studies – preterm birth (N=578).

P_1	Differences in proportions of preterm birth ($P_2 - P_1$)									
	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%
11%	0.11	0.30	0.55	0.77	0.91	0.97	0.99	1	1	1
13%	0.11	0.27	0.50	0.73	0.88	0.96	0.99	1	1	1
15%	0.10	0.25	0.47	0.69	0.85	0.95	0.98	1	1	1
17%	0.10	0.23	0.44	0.66	0.83	0.93	0.98	0.99	1	1
19%	0.09	0.22	0.41	0.63	0.81	0.92	0.97	0.99	1	1
21%	0.09	0.21	0.39	0.60	0.78	0.90	0.96	0.99	1	1
23%	0.09	0.20	0.38	0.58	0.76	0.89	0.96	0.99	1	1
25%	0.09	0.19	0.36	0.56	0.75	0.88	0.95	0.98	1	1
27%	0.08	0.19	0.35	0.55	0.73	0.87	0.95	0.98	1	1
29%	0.08	0.18	0.34	0.53	0.72	0.86	0.94	0.98	0.99	1

P_1, proportion of preterm birth in HIV-negative women; P_2, proportion of preterm birth in HIV-positive women.

Among single women, those with HIV were older, less educated, more likely to be parous, had less frequent antenatal care (ANC) visits, had higher proportions of women with inadequate GWG in the second trimester and genital tract infection, and had lower haemoglobin level in the third trimester compared with those without HIV (Appendix 6.1: Table 6.1). However, among married/cohabiting women, those with HIV were recruited at an earlier gestational age and had lower a haemoglobin level in the third trimester compared with those without HIV (Appendix 6.1: Table 6.1). Furthermore, among HIV-positive women whose data

included antenatal CD4 counts (n=106), those who were single had lower CD4 counts than those who were married/cohabiting (Appendix 6.1: Table 6.2). These data may partly explain why treated maternal HIV infection increased PTB risk in single women. A meta-analysis has reported that a woman's relationship with her baby's father is a predictor of PTB: single women have the highest risk compared with married and cohabiting women [526]. For single women, the pregnancy could become a stressful and difficult life experience due to a partner's lack of emotional support and safety guarantees, inadequate social support, anxiety about the future and financial constraints [527-531]. These could induce prolonged maternal prenatal stress that has been linked with the activation of hypothalamic-pituitary-adrenal (HPA) responses, the release of cortisol hormone and, in turn, shortened gestation [532-536].

The association between parity and PTB has been inconsistent. The present finding – an increased risk of PTB in nulliparous compared to parous women – is similar to some previous African studies [516,522], but not others [14,514,525]. The mechanisms through which nulliparity increases PTB risk are still poorly understood [537-539]; several hypotheses have been proposed. First, younger women in a first pregnancy may experience more prenatal stress that has been associated with PTB via the HPA axis [532-536]. In the present study, nulliparous women were younger than parous women (median age: 26 versus 32 years, P=<0.001); however, factors related to prenatal stress were not collected. Being single has been considered as a rough proxy of prenatal stress [540]; in the present study, nulliparous women were more likely to be single than parous women (70.6% versus 57.5%, P=0.024). Second, nulliparity has been associated with a

higher incidence of gestational hypertension [538,539]. However, in the present study, the incidence of gestational hypertension was comparable between nulliparous (9.4%) and parous women (9.7%), $P = 0.936$.

The present finding of an association between a history of ≥2 miscarriages and an increased risk of PTB is consistent with previous studies [541-544]. The explanations remain unclear. Existing evidence suggests that recurrent miscarriage is associated with gestational hypertension, placental abruption, placenta praevia and preterm prelabour rupture of membranes [543,545]. In addition, the surgical management of miscarriage may result in cervical incompetence [542,545].

In women with a prior PTB, the risk of recurrent PTB ranges from 15% to >50% [483]. The present study has shown that the odds of women with a prior PTB having another were more than twice as high as the odds of those without a prior PTB – a finding that confirms previous African studies [515,522,546]. The mechanisms of recurrent PTB remain elusive [483,515,522,546]. The recurrence risk is inversely related to the gestational age of the previous preterm pregnancy [483], which was not collected in the present study. Women with a previous spontaneous PTB are more likely to have another; similarly, women with a previous indicated PTB are more likely to have it repeated in the subsequent pregnancy [483]. Furthermore, short inter-pregnancy interval (<12 months) has been linked with an increased recurrence risk [547,548].

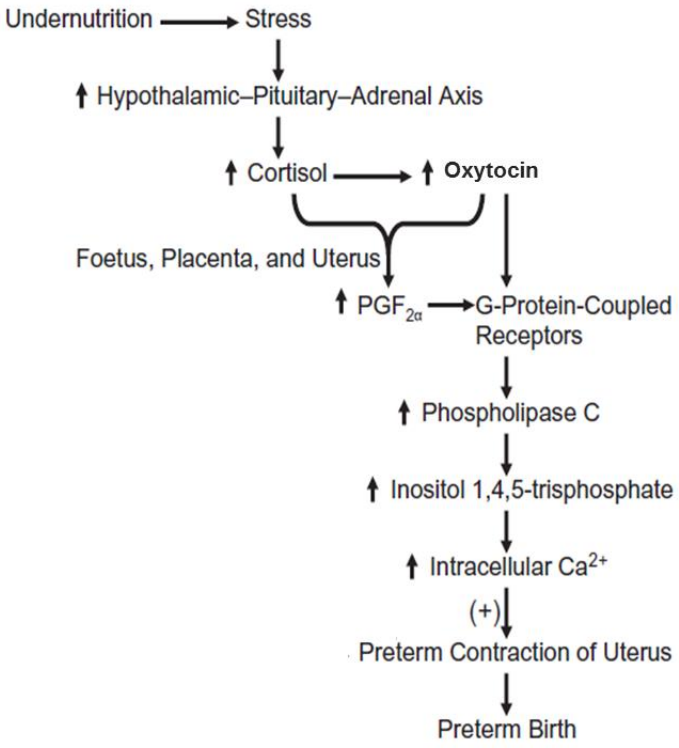


Figure 6.4. Biological mechanisms for undernutrition-induced preterm birth (Wu et al. [549]). Abbreviations: $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; Ca, calcium.

Women with inadequate GWG in the second trimester had approximately twice the risk of having PTB compared to women with adequate GWG. The possible explanations include micronutrient deficiencies, insufficient expansion of plasma volume and higher susceptibility to infection or inflammation [549-551]. Furthermore, maternal undernutrition during pregnancy is a stressor that stimulates the activation of the HPA axis and the production of cortisol, oxytocin and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Figure 6.4). High levels of oxytocin and $PGF_{2\alpha}$ trigger a cell signaling cascade leading to uterine contractions and PTB [549] (Figure 6.4). The pattern of GWG varies throughout pregnancy with the lowest in the first trimester, reaching a peak in the second trimester and declining in the third trimester [552]. Given that the second trimester is the most critical period for

total GWG, gaining less weight during this period may induce the highest levels of cortisol, oxytocin and $PGF_{2\alpha}$, although this explanation is highly speculative.

The present study has shown that gestational hypertension increased the odds of PTB by approximately 80%; however, this finding was borderline significant due to limited statistical power, as indicated by the wide CIs (Table 6.5). Previous African studies had shown a significant association [485,513,520,522,546,553]. Gestational hypertension has been associated with high circulating levels of maternal endothelial dysfunction markers (soluble vascular cell adhesion molecule 1, sVCAM-1; soluble fms-like tyrosine kinase 1, sFlt-1) and low availability of nitric oxide in the fetal endothelium – promising biological markers for (spontaneous) PTB [549,554]. Furthermore, gestational hypertension predisposes to indicated PTB. In the present study, the rate of Caesarean section in women with gestational hypertension was higher than in those without gestational hypertension (75.9% versus 55.7%, P=0.004).

In HIV-negative women, the risk factors for PTB included nulliparity, ≥2 previous miscarriages and history of PTB. However, for nulliparity and history of PTB, the results were borderline significant. In HIV-positive women, the risk factors for PTB included nutritional factors: inadequate GWG in the second and third trimesters; pre-pregnancy BMI was a protective factor. See below (6.5.3 Maternal HIV/ART, nutrition and perinatal outcomes) for further discussion.

6.5.2 Risk factors for small for gestational age

Treated maternal HIV infection was associated with an approximately 60% increase in the odds of SGA. Other risk factors in all women included nulliparity (borderline), history of termination of pregnancy and inadequate GWG in the third trimester; pre-pregnancy BMI was a protective factor.

Table 6.24. Hypothetical scenario of power calculations for future studies – small for gestational age (N=568).

P_1	Differences in proportions of small for gestational age ($P_2 - P_1$)									
	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%
11%	0.11	0.29	0.54	0.76	0.90	0.97	0.99	1	1	1
13%	0.11	0.27	0.50	0.72	0.88	0.96	0.99	1	1	1
15%	0.10	0.25	0.46	0.68	0.85	0.94	0.98	1	1	1
17%	0.10	0.23	0.43	0.65	0.82	0.93	0.98	0.99	1	1
19%	0.09	0.22	0.41	0.62	0.80	0.91	0.97	0.99	1	1
21%	0.09	0.20	0.39	0.60	0.78	0.90	0.96	0.99	1	1
23%	0.09	0.20	0.37	0.57	0.76	0.89	0.96	0.99	1	1
25%	0.08	0.19	0.36	0.56	0.74	0.87	0.95	0.98	1	1
27%	0.08	0.18	0.34	0.54	0.73	0.86	0.94	0.98	0.99	1
29%	0.08	0.18	0.33	0.53	0.71	0.85	0.94	0.98	0.99	1

P_1, proportion of small for gestational age in HIV-negative women; P_2, proportion of small for gestational age in HIV-positive women.

The present finding of an association between treated maternal HIV infection and SGA is consistent with the meta-analysis in Chapter 3. However, the wide CIs (Table 6.16) suggested that the present finding had inadequate statistical power. Table 6.24 shows power calculations for a future study with the same characteristics and sample size as the present study (568 women: 359 HIV-negative, 209 HIV-positive). The proportion of SGA in HIV-negative women in the present study was 16.2% (Figure 6.3). If the proportion in HIV-negative women (P_1) in a future study was 15% or 17%, adequate statistical power of

around 80% would be observed if the proportion of SGA in HIV-positive women (P_2) was 25% or 27% (Table 6.24). The possible mechanisms of adverse perinatal outcomes in treated HIV-positive women are discussed in Chapters 3 and 5.

The borderline significant association between nulliparity and an increased risk of SGA in the present study differed from the previous African studies [449,523], which reported a significant association. A possible explanation for this association, namely young maternal age, characterised by incomplete physical growth (lower stature and smaller pelvic dimensions) may lead to impaired fetal growth [448,449,539,555].

The present finding of an association between prior termination of pregnancy and a higher SGA risk is consistent with several studies [556,557], but not with others conducted in non-HIV settings [558,559]. The biological plausibility for this association remains unclear. Several mechanisms have been proposed, e.g. infection, mechanical trauma to the cervix and scarred tissue following curettage [556-560].

In the present study, SGA was significantly more common in women with inadequate GWG than those with adequate GWG in the third trimester. This finding is similar to the previous studies conducted in Bangladesh [561] and Canada [562], but different from one in the US [563]. Other previous studies conducted in both low and middle-income [518,564-566] and high-income countries [567-570] reported an association between inadequate GWG in the second-third trimester (combined) and an increased risk of SGA. Maternal undernourishment during pregnancy can lead to nutrient imbalances, endocrine

and metabolic disorders and oxidative stress – the changes that may result in impaired placental growth and reduced utero-placental transfer of nutrients and oxygen [549] (Figure 6.5). In the third trimester, the fetus grows most rapidly [552,571] and, therefore, the placenta becomes most active in transferring nutrients to the fetus [561].

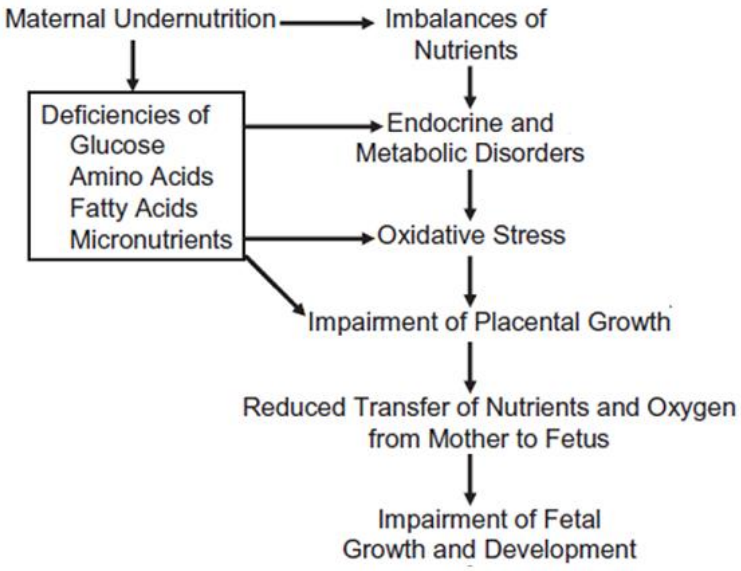


Figure 6.5. Biological mechanisms for undernutrition-induced small for gestational age (Wu et al. [549]).

Each additional 1kg/m^2 of pre-pregnancy BMI was associated with a 7% reduction in the odds of having an SGA baby - a similar finding to a previous study in China [572]. Some studies [518,573,574] have shown that pre-pregnancy underweight was associated with a higher SGA risk, whereas pre-pregnancy overweight was associated with a lower SGA risk. Other studies [575-577], however, have shown that both being underweight and overweight were not associated with SGA. Low pre-pregnancy BMI reflects chronically insufficient energy intake, which could reduce fat and protein deposits; if this energy deficiency persists during pregnancy, the energy to supply the demands of fetal

growth would not be available [572,578]. Furthermore, as mentioned above, maternal undernutrition during pregnancy has been linked with impaired placental growth, which could reduce nutrients and oxygen transfer from the maternal circulation to the fetus [549,578].

In HIV-negative women, the risk factors for SGA included being single (borderline) and ≥2 previous miscarriages. The haemoglobin level in the second trimester was a protective factor: each additional 1g/dL of second-trimester haemoglobin was associated with an approximately 20% decrease in the odds of having an SGA baby. The second trimester is characterised by low haemoglobin concentrations due to physiological haemodilution. According to the World Health Organization (WHO), the haemoglobin threshold for diagnosing mild anaemia in the first and third trimesters is 11g/dL; in the second trimester, the level is 10.5g/dL [78]. Among HIV-negative women in the present study, those with an SGA baby were more likely to be anaemic than those with an appropriately grown baby: mild anaemia, 29.8% versus 13.4%; moderate (haemoglobin 7–9.9g/dL)/severe anaemia (haemoglobin <7g/dL), 12.3% versus 7.5%; *P*=0.002. A meta-analysis [579] has shown that moderate/severe anaemia, but not mild anaemia, is associated with a higher risk of SGA. Some biological mechanisms linking maternal anaemia to SGA have been proposed: 1) low haemoglobin levels create an environment of oxidative stress or chronic hypoxia; 2) iron deficiency stimulates the production of norepinephrine and corticotropin-releasing hormone, which in turn restricts fetal growth [580].

In HIV-positive women, the risk factors for SGA were a history of termination of pregnancy and inadequate GWG in the third trimester. However, excessive GWG in the second trimester was a protective factor (borderline). See below (6.5.3 Maternal HIV/ART, nutrition and perinatal outcomes) for further discussion.

6.5.3 Maternal HIV/ART, nutrition and perinatal outcomes

Figure 6.2 shows that approximately 37% of pregnant women in the present study were HIV-positive. This finding is slightly higher than the previous study conducted in Soweto (33%) [581], but similar to another in Cape Town (38%) [582].

The relationships between maternal HIV/ART, pre-pregnancy BMI, GWG and perinatal outcomes (PTB and SGA) are very complex. The first case of HIV was reported as "slim disease" in 1985 [106]; suggesting that without treatment, chronic HIV infection is characterised by severe weight loss and underweight. However, despite being severely impacted by HIV, the rates of overweight and obesity have actually increased substantially in South Africa, especially in women of child-bearing potential (aged 18–44 years) – these rates are the highest in sub-Saharan Africa [575,582,583]. This is in part attributed to a nutrition shift (from a traditional to a Western diet pattern), sedentary lifestyle and long-term ART exposure [575,582,583]. Previous studies from sub-Saharan Africa have shown a high burden of overweight and obesity in HIV-positive patients after initiating ART, and women have a higher risk of being overweight/obese than men [584-586]. In the present study, the overall median (IQR) of pre-pregnancy BMI was 26.7 (23.2, 30.1) kg/m^2, without any difference across HIV status (Chapter 5:

Table 5.2). The proportions of pre-pregnancy overweight/obesity in HIV-negative and HIV-positive women were 64.8% and 60%, respectively (Appendix 6.2: Table 6.3). The multiple linear regression controlling for several covariates showed that treated maternal HIV infection was not associated with pre-pregnancy BMI in the present study (Appendix 6.2: Table 6.4). High pre-pregnancy BMI ($\geq$25kg/m^2) may lead to metabolic dysfunction during pregnancy and a greater risk of adverse perinatal outcomes [582]. Maternal HIV and ART may also influence metabolic function independently. However, little is known about how the combination of high pre-pregnancy BMI and maternal HIV/ART may affect perinatal outcomes.

In the present study, among HIV-positive women, being single and nulliparity were associated with a lower pre-pregnancy BMI; however, alcohol consumption was associated with a higher pre-pregnancy BMI (Appendix 6.2: Table 6.5). Chapter 5 (Table 5.2) has shown that HIV-positive women were more likely to be single than HIV-negative women, and being single has been used as a rough proxy of prolonged prenatal stress [540]. These may partly explain why every 1kg/m^2 increase in pre-pregnancy BMI was associated with an approximately 10% decrease in the odds of PTB in HIV-positive but not HIV-negative women (Table 6.13).

Chapter 5 (Table 5.2) has shown that treated HIV-positive women were more likely to have inadequate GWG, whereas HIV-negative women were more likely to have excessive GWG in the second and third trimesters. These findings are consistent with the previous study conducted in Soweto [581]. The multiple linear

regression adjusting for several covariates showed that, in the present study, being HIV-positive was negatively associated with rate of GWG (kg/week) in the second (adjusted β: -0.05, 95% CI: -0.09, -0.01) and third trimesters (adjusted β: -0.05, 95% CI: -0.10, 0.00; borderline) (Appendix 6.2: Table 6.6). Among HIV-positive women, alcohol consumption and pre-pregnancy BMI were negatively associated with GWG rate in the second trimester (Appendix 6.2: Table 6.7). The previous study in Cape Town [582] also reported a negative association between pre-pregnancy BMI and GWG. Socio-demographic factors – such as maternal age, education, marital status, smoking and SES – may also influence the rate of GWG in HIV-positive women; however, the limited sample size might have hindered these findings. In addition, the effects of maternal dietary patterns (Western, traditional and mixed) on GWG have been reported by the previous study from Soweto [581], which was conducted at the same hospital as the present study. The Western pattern – characterised by high factor loadings for energy dense, processed, high sugar/fat foods – was associated with a higher rate of GWG in normal weight women. The traditional pattern – with high factor loadings for beans and legumes, vegetables, traditional meats and porridge/pap – was inversely associated with GWG rate in normal-weight women. Mixed pattern – with high factor loadings for both healthy foods (whole grains, nuts and dairy) and sugar items – was positively associated with GWG rate in all women, irrespective of pre-pregnancy BMI category [581]. Nevertheless, this previous study [581] was unable to show whether these effects differed by HIV status.

6.5.4 Strengths and limitations

A number of strengths of this study are worth mentioning. First, to my knowledge, this is the first study in sub-Saharan Africa investigating risk factors for PTB and SGA in HIV-negative and HIV-positive women with accurately determined gestational age and birth weight. This enabled the present study to identify the key risk factors for PTB and SGA in the general population and specific populations by HIV status, and to compare whether these risk factors were different. Second, missing data lead to listwise deletion (i.e. complete-case analysis), reduced sample size and statistical power, and in turn biased estimates. In the present analysis, missing data were handled using multiple imputation (Chapter 5: 5.3.8 Statistical analysis), which has been acknowledged as the most accurate technique for dealing with the issue [587]. Sensitivity analyses comparing the results from complete-case analysis and multiple imputation were also performed. Third, in the present study, the rates of GWG in the second and third trimesters were analysed separately, unlike the previous studies [581-583] which analysed GWG as the rate of total GWG: (weight at last pregnancy visit – weight at recruitment)/duration of follow-up. Given that the highest GWG occurs in the second trimester [552], the use of total GWG may have masked different GWG rates in the second versus third trimester on perinatal outcomes. Other strengths of the present study are provided in Chapter 5.

Some limitations should be considered when interpreting the present findings. First, limited sample size and statistical power – as judged by the wide CIs – might have contributed to: 1) the borderline significant associations of treated maternal HIV infection and other risk factors (gestational hypertension and parity)

with perinatal outcomes; 2) an inability to analyse spontaneous and indicated PTBs separately; 3) an inability to identify more risk factors for perinatal outcomes in each HIV-negative and HIV-positive group; and 4) inadequate exploration of the relationships between maternal HIV/ART, pre-pregnancy BMI, GWG and perinatal outcomes. Second, the effect of GWG in the first trimester on perinatal outcomes was not assessed because information on pre-pregnancy weight was not available in some women. Third, information was not collected on the techniques used and timing (first, second or third trimester) of previous pregnancy termination, which may have different effects on perinatal outcomes [556,559]. Fourth, precise information about the gestational age and type of previous PTB (spontaneous or indicated) was not captured in the present study. This made it more difficult to explain the association between history of PTB and a higher PTB risk in the subsequent pregnancy [483]. Fifth, information on maternal HIV/ART (stage of HIV disease, timing of ART initiation, ART regimen and CD4 count) was not available for all HIV-positive women, which prevented the identification of maternal HIV/ART-related risk factors. Sixth, other risk factors, such as maternal prenatal stress and dietary patterns, which have been reported as a predictor of perinatal outcomes [532,583], were not assessed in the present study. Seventh, the present hospital-based study was conducted at the largest referral hospital in Africa; the findings could be different if the present study was population-based. Other potential limitations of the present study are provided in Chapter 5.

6.5.5 Implications of findings

The present study has shown several traditionally established modifiable (treated maternal HIV infection, low pre-pregnancy BMI, inadequate GWG in the second and third trimesters and low haemoglobin level in the second trimester) and non-modifiable (single marital status, nulliparity, ≥2 previous miscarriages, histories of PTB and termination of pregnancy and gestational hypertension) risk factors for PTB and/or SGA in South Africa. In HIV-negative women, the risk factors were being single, nulliparity, ≥2 previous miscarriages, history of PTB and low haemoglobin level in the second trimester. In HIV-positive women, the risk factors were history of termination of pregnancy, inadequate GWG in the second and third trimesters and low pre-pregnancy BMI. These findings should provide guidance for future studies and practice.

6.5.5.1 Implication for future studies

First, consistent with Chapters 3 and 5, ongoing surveillance is imperative to provide updated evidence for the complex relationships between maternal HIV/ART, maternal health and perinatal outcomes, especially in a country with the highest HIV prevalence globally. Second, larger and high-powered studies will offer several advantages: 1) adequate assessments and firm conclusions for the associations of treated maternal HIV infection and other maternal risk factors with PTB and SGA; 2) an opportunity to distinguish spontaneous from indicated PTB, which have different biological plausibility [483], especially in HIV-positive women [411]; 3) a more nuanced risk factor analysis in HIV-negative and HIV-positive groups; 4) a more profound exploration of why pre-pregnancy BMI and GWG were key risk factors for PTB and SGA in HIV-positive women, but

not in HIV-negative women. Third, in order to obtain a complete picture of the effect of GWG across trimesters of pregnancy on perinatal outcomes, information on pre-pregnancy weight is crucial to estimate the rate of GWG in the first trimester. This information is also needed to calculate pre-pregnancy BMI more accurately. Fourth, the finding that more than 30% of women had inadequate GWG in the second and third trimesters (Table 6.1) highlights the need to investigate the reasons for such a high rate. There was a large difference between the rates of pre-pregnancy underweight (1.7%) (Appendix 6.2: Table 6.3) and inadequate GWG in the second (36.3%) and third trimesters (30.2%) (Table 6.1), suggesting that food insecurity is not the main contributor for inadequate GWG in this population. Therefore, future studies should investigate other factors such as prenatal stress that may impair appetite during pregnancy. However, the negative associations between pre-pregnancy BMI and PTB (in HIV-positive women) and SGA (in all women) suggest that the importance of adequate pre-pregnancy nutrition should not be disregarded. Fifth, clarifying how GWG is driving perinatal outcomes in each pre-pregnancy BMI stratum will be useful to develop prenatal nutritional interventions. Existing studies [563,569] have shown that, in the context of perinatal outcomes, inadequate GWG may be safe or even beneficial for overweight and obese women. Therefore, the association between GWG and perinatal outcomes in each pre-pregnancy BMI stratum should be assessed in this study population. Sixth, studies with a larger sample size of HIV-positive women with complete information on HIV/ART are needed to establish more determinants of perinatal outcomes in HIV-positive women. In addition, information on maternal HIV/ART is useful to better explain the intricate

associations between maternal HIV/ART, pre-pregnancy BMI, GWG and perinatal outcomes. It is possible that, in HIV-positive pregnant women, pre-conception and post-conception initiation of ART affect GWG differently [582,588]. Seventh, for studies aiming to explore the effect of prior pregnancy termination and perinatal outcomes further, information on techniques used and timing of previous pregnancy termination would be beneficial. Eighth, for studies aiming to better understand why history of PTB increases PTB risk in the subsequent pregnancy, information related to the previous PTB – gestational age and type of PTB – would be useful. Ninth, large prospective population-based studies evaluating risk factors assessed in the present study will provide valuable guidance for the development of public health interventions geared towards improving perinatal outcomes in South Africa.

6.5.5.2 Implication for practice

Overall, the rates of pre-pregnancy overweight/obesity (63%, Appendix 6.2: Table 6.3) and treated maternal HIV infection (37%, Figure 6.2) were relatively high in the present study. ART initiation has been associated with a higher rate of overweight/obesity, especially in HIV-positive women [584-586]. These highlight the need for weight management interventions (i.e. dietary counselling, regular physical activity and healthy lifestyle) before pregnancy to ensure a healthy BMI.

In the present hospital-based study, ANC was started very early (<14 weeks' gestation) and scheduled every 5±1 weeks; however, women in sub-Saharan Africa commonly present late for ANC services [13,97]. Therefore, intensified health education targeting early ANC is required, especially for younger

nulliparous women. The ANC services should provide counselling regarding healthy pregnancy, hygiene practices and risk factors predisposing women to have babies with adverse perinatal outcomes. The importance of a woman's obstetric history – such as history of miscarriages, termination of pregnancy and PTB – as risk factors for PTB and SGA should be better appreciated. Furthermore, screening for pregnancy complications, e.g. anaemia and gestational hypertension, should be performed and affected women managed appropriately. For HIV-positive women, the importance of ART adherence in improving maternal health and thus reducing HIV comorbidity should be emphasised.

Interventions promoting adequate GWG across trimesters of pregnancy are urgently needed as part of routine ANC, for example, by providing counselling regarding weight gain control and nutritional plan during pregnancy. These interventions should be individualised according to pre-pregnancy BMI.

Current evidence has shown that maternal prenatal stress is proxied by single marital status [540]. Approximately 61% of women in the present study were single (Table 6.1). Therefore, the present study highlights the need for interventions focusing on: 1) early detection of maternal prenatal stress; 2) stress-reduction strategies, i.e. organising ANC groups, social and emotional support (especially for single women), education and empowerment [540].

Chapter 7: Fetal growth patterns according to maternal HIV status and timing of ART initiation.

7.1 Introduction

Chapters 3, 5 and 6 have described the associations between treated maternal HIV infection and risk of adverse perinatal outcomes and the observation that maternal HIV and antiretroviral therapy (ART) may have detrimental effects on the mother, fetus and placenta – the three main regulators of fetal growth (Chapter 2: Table 2.15 and Figure 2.30). However, in HIV-settings, fetal growth is generally assessed using surrogate measures: birth weight as a proxy for fetal growth [589] and small for gestational age (SGA) as a proxy for fetal growth restriction [590,591]. Such cross-sectional birth weight data are only an index of newborn size, and do not necessarily convey the pattern of longitudinal fetal growth throughout pregnancy. Various fetal growth patterns may result in the same birth weight, i.e. similar birth weights may represent both healthy and impaired fetal growth.

In order to more accurately estimate and assess fetal growth patterns, fetal biometric parameters (biparietal diameter, BPD; head circumference, HC; abdominal circumference, AC; and femur length, FL) measured longitudinally across gestation are needed. To my knowledge, studies with such fetal biometric

measurements have never been conducted in HIV settings; most existing studies were conducted in non-HIV settings in high-income countries [303-307,592,593].

7.2 Aim

This chapter aims to compare fetal growth patterns by maternal HIV status and timing of ART initiation in a prospective longitudinal study with repeatedly measured fetal biometric parameters in South Africa, a resource-limited setting with the largest HIV epidemic globally and a high HIV prevalence and ART coverage in pregnant women.

7.3 Methods

Descriptions of the study setting and design, participants, data collection and ethical considerations are provided in Chapters 4 and 5. Definitions of the exposures of interest, i.e. treated maternal HIV infection and timing of ART initiation, and additional covariates including maternal age, education, marital status, smoking, alcohol consumption, socio-economic status (SES), pre-pregnancy body mass index (BMI), parity, history of adverse perinatal outcomes and fetal sex are provided in Chapter 5.

7.3.1 Outcomes of interest

The outcomes of interest were growth trajectories of fetal BPD, HC, AC and FL across pregnancy. Following the dating scan at <14 weeks' gestation, women were scheduled for up to six follow-up visits at five weekly (±1 week) intervals until delivery. At each visit, the measurements of fetal biometric parameters were performed (Chapter 4: Figure 4.1). BPD and HC were measured at a cross-

sectional view of the fetal head at the level of the thalami. For BPD, the intersection of the calipers was placed on the outer border of the parietal bones ('outer to outer') at the widest part of the skull. HC was measured using the ellipse facility placed along the outer border of the skull. AC was measured at a transverse section of the fetal abdomen as close as possible to circular, using the ellipse facility placed along the outer border of the abdomen. FL was measured as close as possible to the horizontal plane; the intersection of the calipers was placed on the outer borders of the edges of the femoral bone ('outer to outer').

7.3.2 Statistical analysis

Maternal/fetal characteristics were compared by maternal HIV status (HIV-negative versus HIV-positive), and by timing of ART initiation (pre-conception versus post-conception ART) among the HIV-positive group, as in Chapter 5. The raw data of fetal biometry were plotted and superimposed onto the 3rd, 10th, 50th, 90th and 97th centiles of the INTERGROWTH-21st Fetal Growth Standards [310]. The analyses were restricted to scans performed at ≥15 and <40 weeks' gestation due to the limited number of scans at 13 (n=1), 14 (n=6), 40 (n=8) and 41 (n=4) weeks' gestation.

The present fetal biometry data comprised two levels: one ultrasound measurement at each visit for each woman during pregnancy (level 1) and all the measurements pooled (level 2), i.e. measurement occasion nested within the women. The growth trajectories of fetal BPD, HC, AC and FL were created by fitting linear mixed models. Linear and non-linear functions of fetal biometry as a function of gestational age were evaluated, i.e. linear, quadratic, fractional

polynomials, cubic, cubic splines and restricted cubic splines with several knot points. The data of treated HIV-positive and HIV-negative women were modeled separately. The most suitable functional form for treated HIV-positive women was restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation), and for HIV-negative women was second-order fractional polynomials. The decision to model treated HIV-positive and HIV-negative data separately was decided *a priori* due to the expected sample size adequate enough to model each precisely. Among HIV-positive women, the data of those initiating ART pre- and post-conception were also modeled separately. The most suitable functional form for pre-conception ART was restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation), and for post-conception ART was second-order fractional polynomials. The comparisons of fetal growth patterns by maternal HIV status and timing of ART initiation were performed: 1) visually by assessing the growth trajectories of fetal BPD, HC, AC and FL and 2) by comparing the predicted values of these biometric parameters at two time points: end of second trimester (i.e. 27 weeks' gestation, see Chapter 5) and at 37 weeks' gestation.

The models were a two-level random intercept and slope model (details of these models are provided in Appendix 7.1: Table 7.1). As an illustration, fetal biometric parameters in HIV-negative women (n=389) were modeled using second-order fractional polynomials (FP2) (Appendix 7.1: Table 7.1), and these models can be written as follows:

$$y_{jk} = \beta_0 + \beta_1 X_1^{p}{}_{1jk} + \beta_2 X_1^{p}{}_{2jk} + \upsilon_{0j} + \upsilon_{1j} X_{jk} + \varepsilon_{jk}$$

For a given fetal biometric measurement of subject j (j = 1, 2, …, 389 women) taken on visit k (k = 1, 2, …, 6 visits), the above equation represents the

regression of fetal biometric parameters (BPD, HC, AC and FL), *y*, on the independent variable, gestational age, in weeks, X. β_1 and β_2 represent the population slopes. The term υ_{0j} is the influence of individual *j* on their repeat measurements taken on visit *k*. For a given group *j*, the intercept is $\beta_0 + \upsilon_{0j}$. The term υ_{1j} represents the slope deviation for each subject *j* from the average regression slopes β_1 and β_2. ε_{jk} is an independent error term distributed normally with mean 0 and variance σ^2. Powers p_1 and p_2 were selected from a restricted set {-2,-1,-0.5,0,0.5,1,2,3} and x^0 denotes log (*x*) rather than $x^0 = 1$.

All models were adjusted for maternal/fetal characteristics defined *a priori* based on the existing literature: maternal age, education, marital status, smoking, alcohol consumption, SES, pre-pregnancy BMI, parity, history of adverse perinatal outcomes and fetal sex [303-306,594]. All these covariates were fitted as fixed effects. All analyses were performed using STATA™ version 15.1 (StataCorp, Texas, USA).

7.4 Results

7.4.1 Fetal growth patterns according to maternal HIV status

Of the 680 women enrolled, 68 (10%) were excluded due to loss to follow-up (n=36), withdrawal of consent (n=11) and without any scan (n=21). Hence, a total of 612 women were analysed: 389 (63.6%) were HIV-negative and 223 (36.4%) treated HIV-positive (Figure 7.1). After excluding 19 scans performed at <15 or ≥40 weeks' gestation, a total of 2,564 scans were analysed: 1,632 scans (63.7%) in HIV-negative and 932 scans (36.3%) in treated HIV-positive women (Figure 7.1).

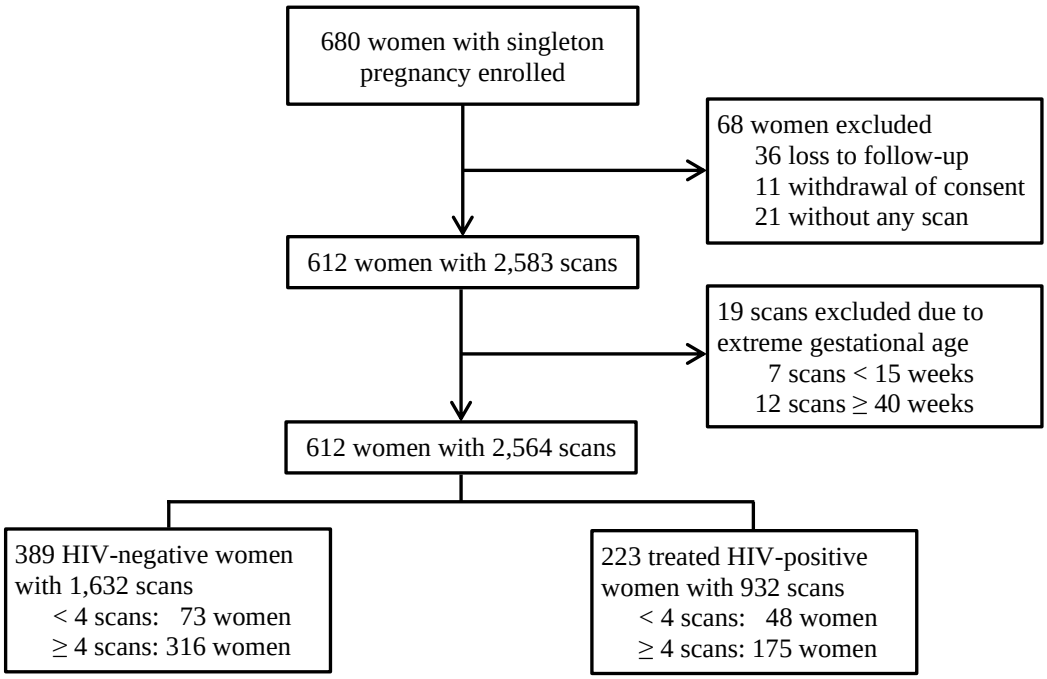


Figure 7.1. Flow diagram of study participants included in the analysis of fetal growth patterns by maternal HIV status. Abbreviation: HIV, human immunodeficiency virus.

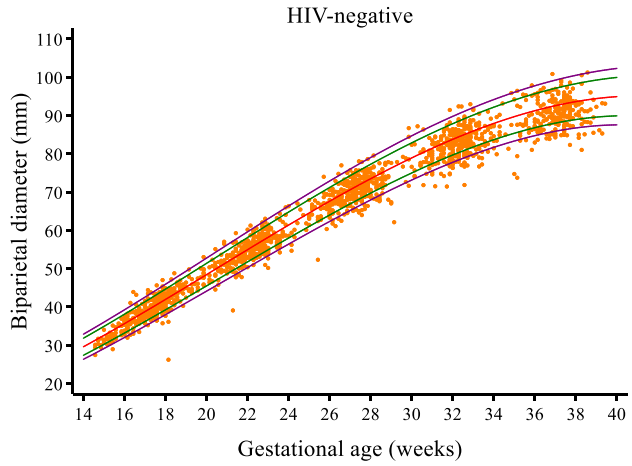
The comparison of maternal/fetal characteristics by maternal HIV status is presented in Table 7.1. Treated HIV-positive women were older, less educated, more likely to be parous, had a lower proportion of women with ≥2 previous miscarriages and had a different distribution of SES compared with HIV-negative women (Table 7.1). Figure 7.2 shows the gestational age-specific observed fetal biometric parameters for HIV-negative and treated HIV-positive women compared to the INTERGROWTH-21st Fetal Growth Standards. The distributions of fetal biometric parameters were fairly similar for HIV-negative and treated HIV-positive women across pregnancy.

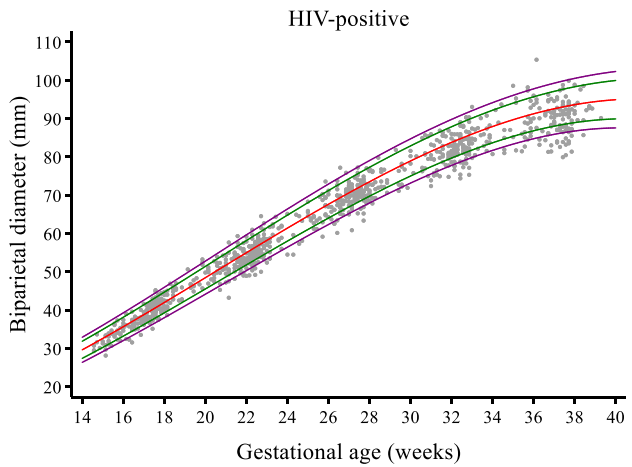
Table 7.1. Maternal/fetal characteristics according to maternal HIV status.

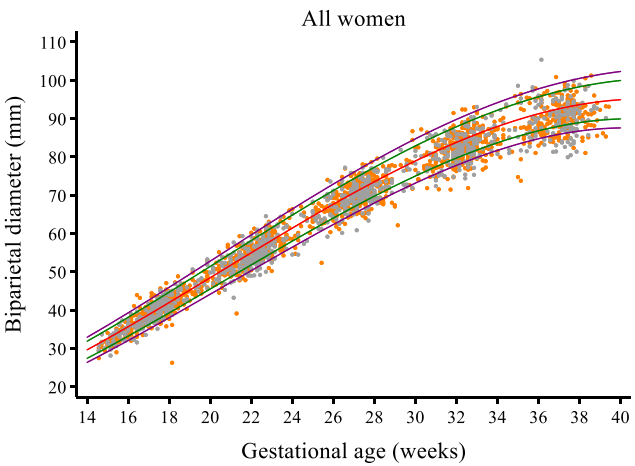
Maternal/fetal characteristics	All women (N=612) n (%)	HIV-negative (N=389) n (%)	HIV-positive (N=223) n (%)	*P* value[§]
Age (years), median (IQR)	31 (26, 35)	30 (26, 34)	32 (28, 37)	<0.001
Education (years), median (IQR)	12 (11, 12)	12 (12, 12)	12 (11, 12)	<0.001
Single	373 (61)	227 (58.4)	146 (65.5)	0.082
Smoked during pregnancy	37 (6.1)	21 (5.4)	16 (7.2)	0.375
Alcohol consumption	49 (8)	28 (7.2)	21 (9.4)	0.330
Socioeconomic status				
Low	118 (19.3)	79 (20.3)	39 (17.5)	0.011
Middle	265 (43.3)	151 (38.8)	114 (51.1)	
High	229 (37.4)	159 (40.9)	70 (31.4)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.7 (23.2, 30.1)	26.8 (23.3, 30.2)	26.4 (22.8, 30.0)	0.630
Nulliparity	96 (16.7)	70 (19.4)	26 (12.2)	0.026
Number of previous miscarriages ≥2	132 (23)	95 (26.3)	37 (17.4)	0.014
History of adverse perinatal outcomes	207 (36.1)	136 (37.7)	71 (33.3)	0.296
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (11, 13)	0.301
Caesarean section	339 (55.4)	214 (55)	125 (56.1)	0.803
Female fetus	274 (47.7)	177 (49)	97 (45.5)	0.419

[§] *P* value from Wilcoxon-Mann-Whitney or chi-square test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
Missing data: <7%.
Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range.

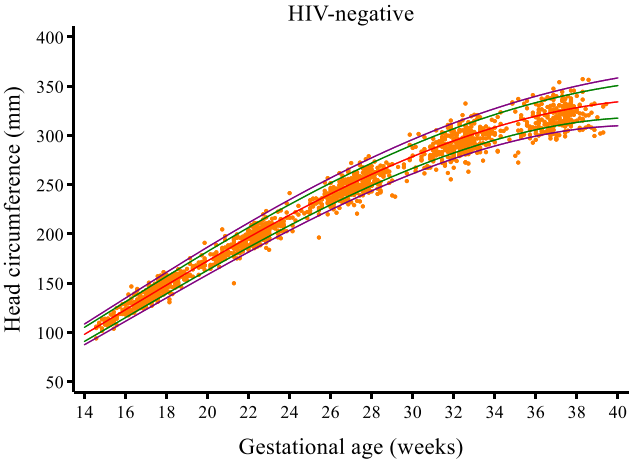
A

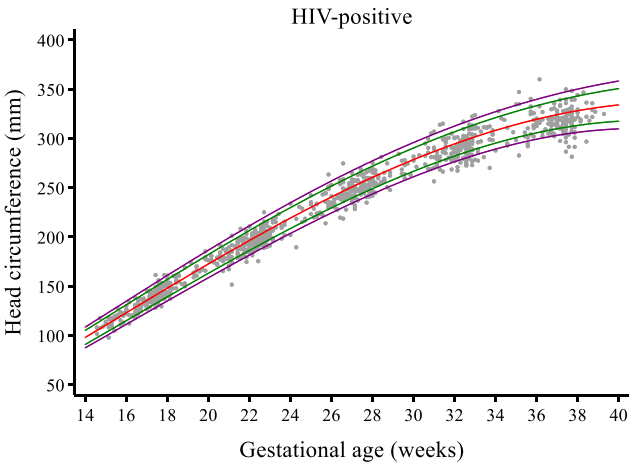

HIV-negative
Biparietal diameter (mm)
Gestational age (weeks)

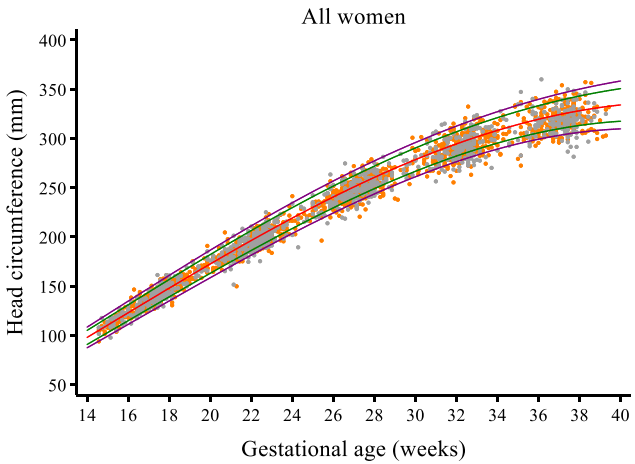

HIV-positive
Biparietal diameter (mm)
Gestational age (weeks)


All women
Biparietal diameter (mm)
Gestational age (weeks)

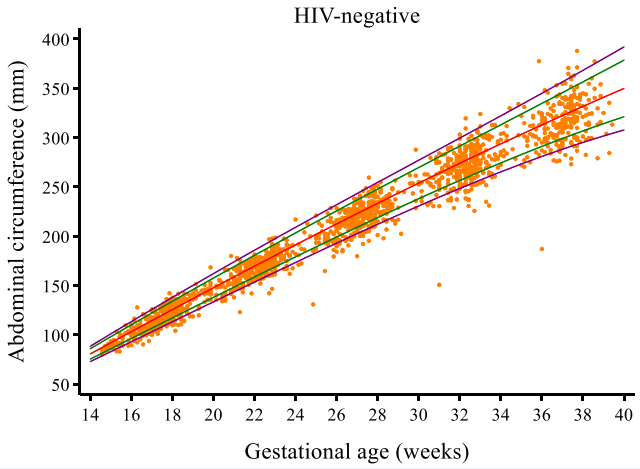
B

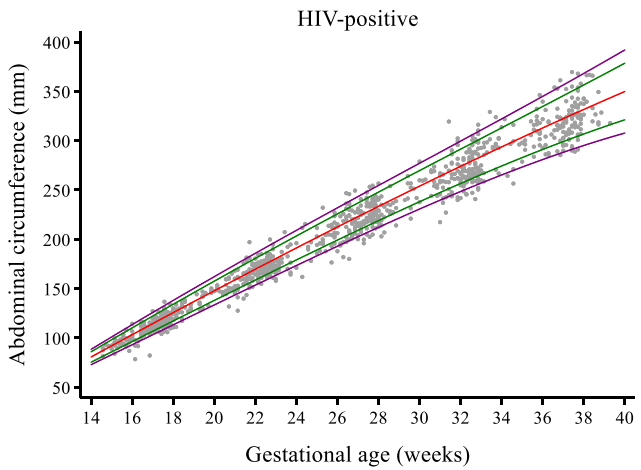

HIV-negative
Head circumference (mm)
Gestational age (weeks)


HIV-positive
Head circumference (mm)
Gestational age (weeks)


All women
Head circumference (mm)
Gestational age (weeks)

C


HIV-negative
Abdominal circumference (mm)
400
350
300
250
200
150
100
50
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)


HIV-positive
Abdominal circumference (mm)
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250
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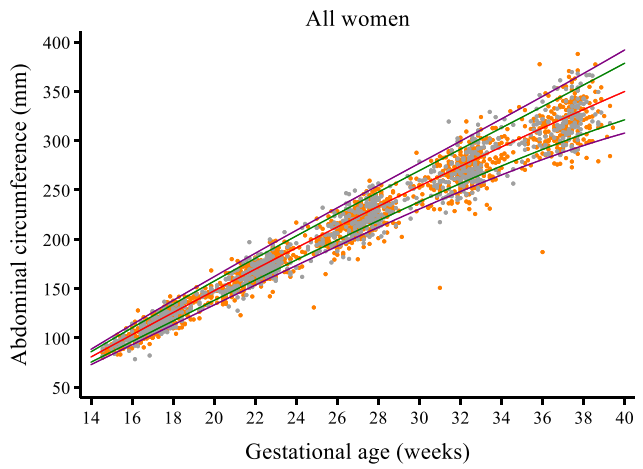
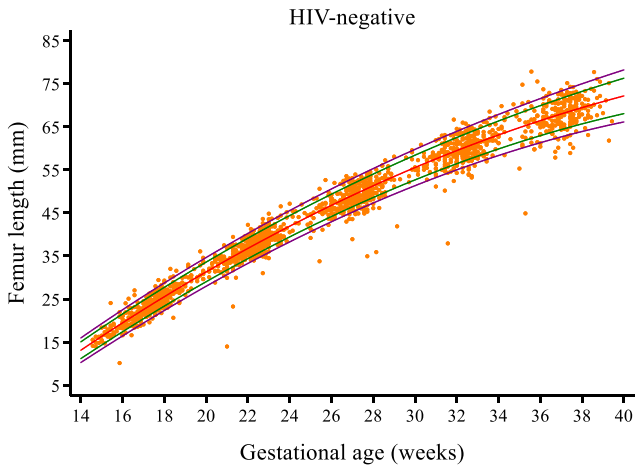
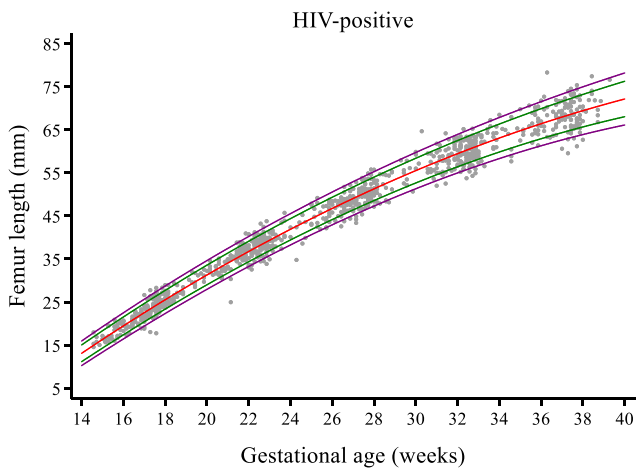
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)


All women
Abdominal circumference (mm)
400
350
300
250
200
150
100
50
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)

D


HIV-negative
Femur length (mm)
85
75
65
55
45
35
25
15
5
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)


HIV-positive
Femur length (mm)
85
75
65
55
45
35
25
15
5
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)

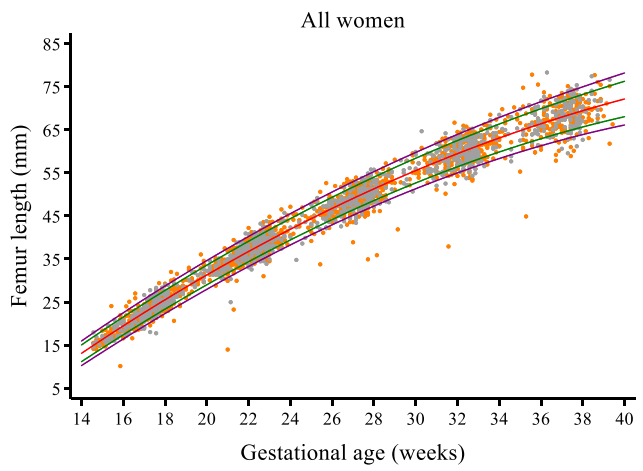

All women
Femur length (mm)
85
75
65
55
45
35
25
15
5
14 16 18 20 22 24 26 28 30 32 34 36 38 40
Gestational age (weeks)

Figure 7.2. Gestational age-specific observed fetal biparietal diameter (A), head circumference (B), abdominal circumference (C) and femur length (D) in HIV-negative women (left, orange), treated HIV-positive women (middle, grey), and HIV-negative and treated HIV-positive women superimposed (right), compared to the INTERGROWTH-21st Fetal Growth Standards. Purple lines indicate 3rd and 97th centiles, green lines 10th and 90th centiles, red line 50th centile in the INTERGROWTH-21st Fetal Growth Standards. Abbreviation: HIV, human immunodeficiency virus.

7.4.1.1 Biparietal diameter (BPD)

The growth trajectories of fetal BPD in treated HIV-positive and HIV-negative women almost overlapped throughout pregnancy (Figure 7.3). Compared to the INTERGROWTH-21st standards, the fetal BPD growth curves of both treated HIV-positive and HIV-negative women were around the 50th centile until approximately 25 weeks' gestation. From 26 to 34 weeks' gestation, the curves dropped steadily: from the 40th to the 19th centile for treated HIV-positive women, and from the 41st to the 24th centile for HIV-negative women. At 39 weeks' gestation, the curves rose to the 39th centile for treated HIV-positive women, and to the 32nd centile for HIV-negative women (Figure 7.3).

The predicted values of fetal BPD at the end of the second trimester and at 37 weeks' gestation were fairly similar for treated HIV-positive and HIV-negative women (Table 7.2). The fetal BPD means by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st Fetal Growth Standards are presented in Appendix 7.2: Table 7.2.

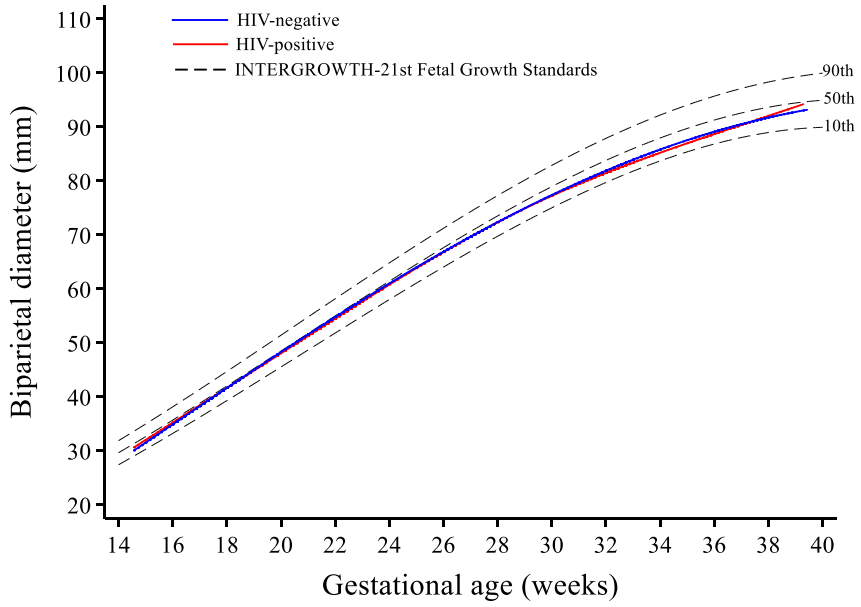


Figure 7.3. Fetal growth trajectories for biparietal diameter by maternal HIV status. The HIV-negative group was fitted using second-order fractional polynomials with powers $p_1 = 2$ and $p_2 = 2$; the HIV-positive group was fitted using restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation). The models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex. Abbreviation: HIV, human immunodeficiency virus.

Table 7.2. The predicted values of fetal BPD at 27 and 37 weeks' gestation by maternal HIV status.

Gestational age	Fetal BPD (mm)	
	HIV-negative	HIV-positive
27 weeks (end of 2nd trimester)	69.7	69.6
37 weeks	90.6	90.5
Abbreviations: BPD, biparietal diameter; HIV, human immunodeficiency virus.		

7.4.1.2 Head circumference (HC)

Figure 7.4 shows that the fetal HC growth trajectories in treated HIV-positive and HIV-negative women almost overlapped across pregnancy. Until about 21 weeks' gestation, the fetal HC growth curves of both treated HIV-positive and HIV-negative women were around the 50th centile of the INTERGROWTH-21st standards. At 22 weeks' gestation, the curves dropped to the 37th centile in treated

HIV-positive women, and to the 43rd centile in HIV-negative women. At 24, 26 and 28 weeks' gestation both curves just overlapped at approximately the 30th, 38th and 30th centiles, respectively (Figure 7.4). From 30 to 37 weeks' gestation, the curves of treated HIV-positive women had lower centiles than those of HIV-negative women (Figure 7.4). For example, at 30, 34 and 37 weeks' gestation, the curves were at the 29th versus 34th centile, 21st versus 30th centile and 29th versus 33rd centile for treated HIV-positive versus HIV-negative women, respectively. At 38 weeks' gestation, both curves overlapped at approximately the 31st centile (Figure 7.4).

At the end of the second trimester, treated HIV-positive and HIV-negative women had similar predicted values of fetal HC. However, at 37 weeks' gestation, treated HIV-positive women had 1.4 mm lower fetal HC than HIV-negative women (Table 7.3). The means of fetal HC by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st Fetal Growth Standards are presented in Appendix 7.2: Table 7.3.

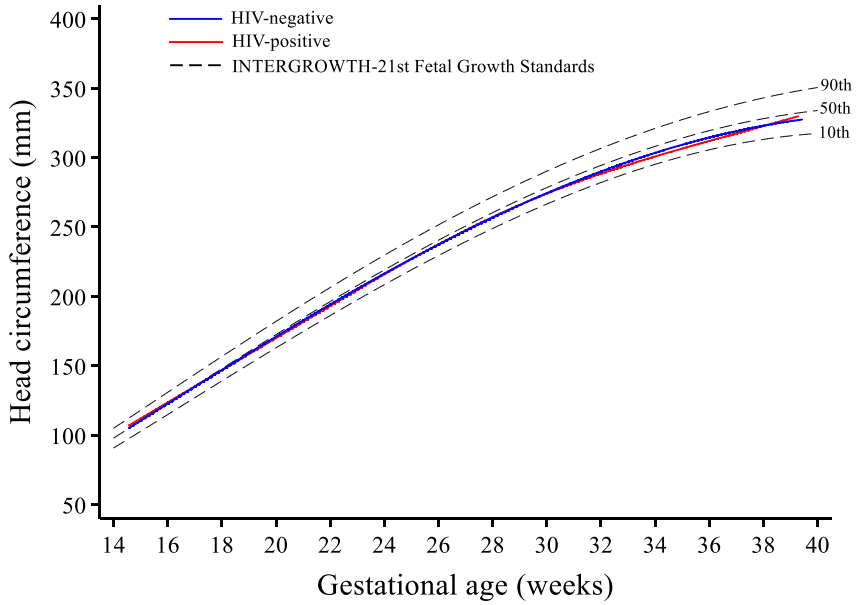


Figure 7.4. Fetal growth trajectories for head circumference by maternal HIV status. The HIV-negative group was fitted using second-order fractional polynomials with powers $p_1 = 2$ and $p_2 = 2$; the HIV-positive group was fitted using restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation). The models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex. Abbreviation: HIV, human immunodeficiency virus.

Table 7.3. The predicted values of fetal HC at 27 and 37 weeks' gestation by maternal HIV status.

Gestational age	Fetal HC (mm)	
	HIV-negative	HIV-positive
27 weeks (end of 2nd trimester)	247.4	247.6
37 weeks	319.3	317.9
Abbreviations: HC, head circumference; HIV, human immunodeficiency virus.		

7.4.1.3 Abdominal circumference (AC)

Overall, the fetal AC growth trajectories in treated HIV-positive women were similar to those in HIV-negative women (Figure 7.5). From 18 weeks' gestation onwards, the fetal AC growth curves for both treated HIV-positive and HIV-negative women were just under the 50th centile of the INTERGROWTH-21st standards. At 18 weeks' gestation, the curves were around the 26th centile for

treated HIV-positive women, and at the 25th centile for HIV-negative women. At 39 weeks' gestation, the curves rose to the 40th centile for treated HIV-positive women, and to the 37th centile for HIV-negative women (Figure 7.5).

The predicted values of fetal AC at the end of the second trimester were similar between treated HIV-positive and HIV-negative women. However, at 37 weeks' gestation, fetal AC was 2.4 mm more in treated HIV-positive women than in HIV-negative women (Table 7.4). The fetal AC means by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st Fetal Growth Standards are presented in Appendix 7.2: Table 7.4.

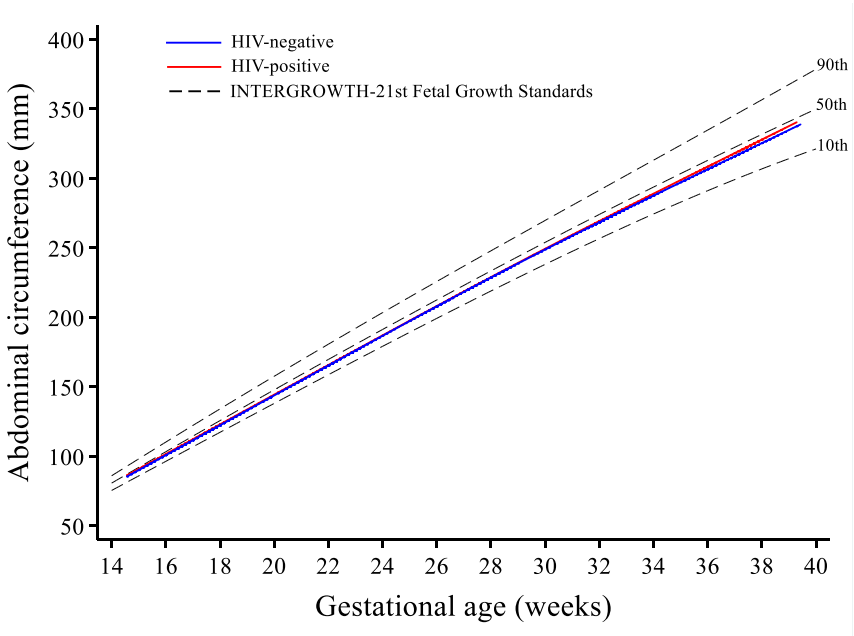


Figure 7.5. Fetal growth trajectories for abdominal circumference by maternal HIV status. The HIV-negative group was fitted using second-order fractional polynomials with powers $p_1 = 1$ and $p_2 = 3$; the HIV-positive group was fitted using restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation). The models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex. Abbreviation: HIV, human immunodeficiency virus.

Table 7.4. The predicted values of fetal AC at 27 and 37 weeks' gestation by maternal HIV status.

Gestational age	Fetal AC (mm)	
	HIV-negative	HIV-positive
27 weeks (end of 2nd trimester)	218.3	218.5
37 weeks	316.5	318.9
Abbreviations: AC, abdominal circumference; HIV, human immunodeficiency virus.		

7.4.1.4 Femur length (FL)

Across pregnancy, the fetal FL growth trajectories in treated HIV-positive and HIV-negative women overlapped around the 50th centile of the INTERGROWTH-21st standards (Figure 7.6).

The predicted values of fetal FL at the end of the second trimester and at 37 weeks' gestation were similar between treated HIV-positive and HIV-negative women (Table 7.5). The fetal FL means by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st Fetal Growth Standards are presented in Appendix 7.2: Table 7.5.

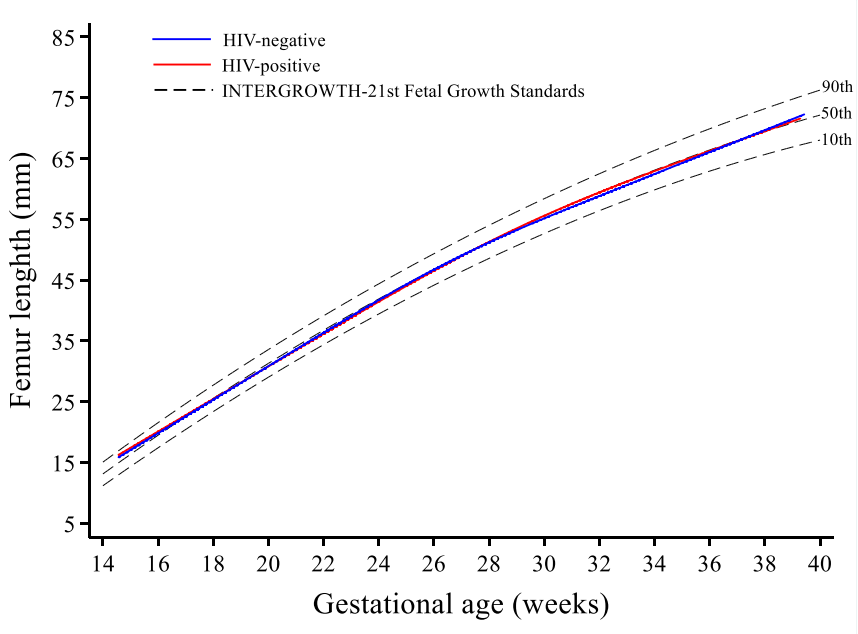


Figure 7.6. Fetal growth trajectories for femur length by maternal HIV status. The HIV-negative group was fitted using second-order fractional polynomials with powers p_1 = 0.5 and p_2 = 3; the HIV-positive group was fitted using restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation). The models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex. Abbreviation: HIV, human immunodeficiency virus.

Table 7.5. The predicted values of fetal FL at 27 and 37 weeks' gestation by maternal HIV status.

Gestational age	Fetal FL (mm)	
	HIV-negative	HIV-positive
27 weeks (end of 2nd trimester)	49.1	48.9
37 weeks	68	68
Abbreviations: FL, femur length; HIV, human immunodeficiency virus.		

7.4.2 Fetal growth patterns according to timing of ART initiation

Of the 223 HIV-positive women included in the present study, 122 (55%) consented to provide detailed information on HIV/ART. The comparisons between HIV-positive women who consented and those who did not consent to provide information on HIV/ART are presented in Chapter 5 – Appendix 5.1: Table 5.1. Of the 122 women, 16 were excluded due to missing information on

timing of ART initiation, a total of 106 HIV-positive women (466 scans) were analysed: 37 initiated ART pre-conception (161 scans) and 69 post-conception (305 scans) (Figure 7.7). The comparisons of maternal/fetal characteristics by timing of ART initiation are provided in Chapter 5 (Tables 5.7 to 5.9).

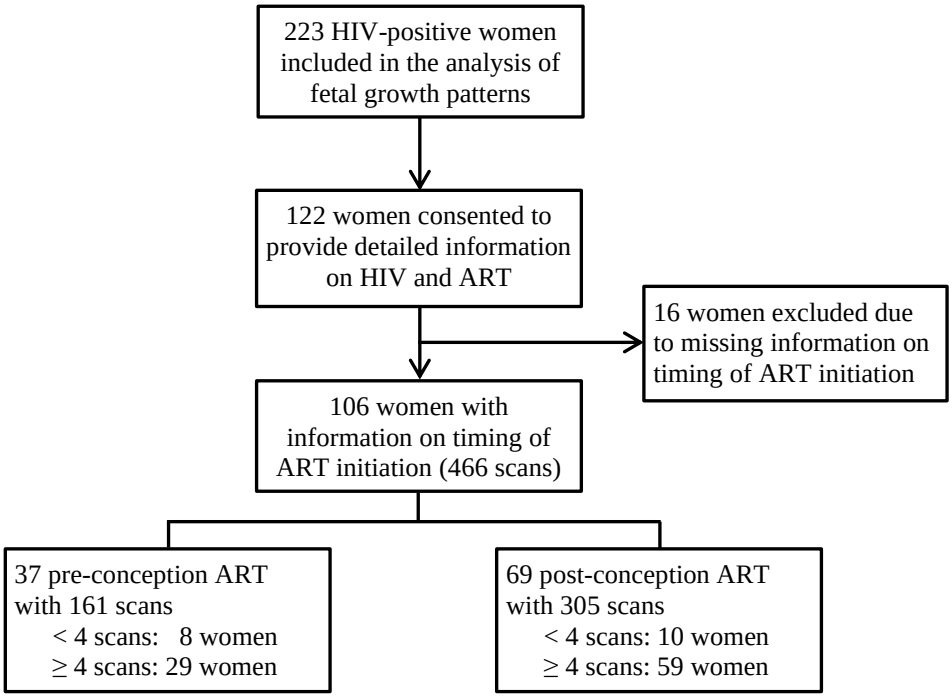


Figure 7.7. Flow diagram of study participants included in the analysis of fetal growth patterns by timing of ART initiation. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Overall, the growth trajectories of fetal BPD, HC, AC and FL in HIV-positive women initiating ART pre-conception were lower than in those initiating ART post-conception (Figure 7.8). Correspondingly, the predicted values of fetal BPD, HC, AC and FL at the end of the second trimester and at 37 weeks' gestation were lower in those initiating ART pre-conception than post-conception (Table 7.6).

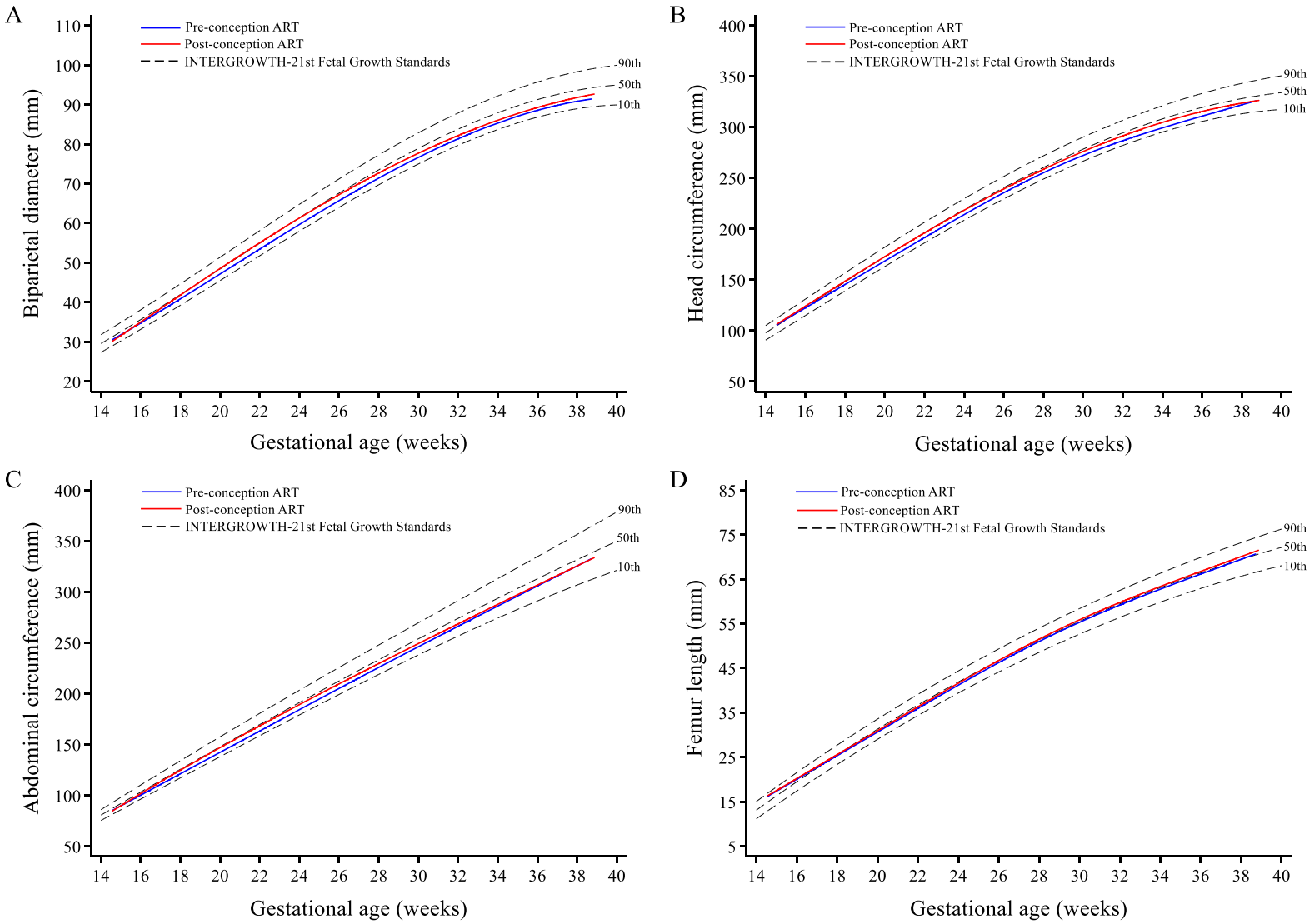


Figure 7.8. Fetal growth trajectories for biparietal diameter (A), head circumference (B), abdominal circumference (C) and femur length (D) by timing of ART initiation. The pre-conception ART group was fitted using restricted cubic splines with three-knot points (21, 29 and 37 weeks' gestation); the post-conception ART group was fitted using second-order fractional polynomials (Appendix 7.1: Table 7.1). The models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex. Abbreviation: ART, antiretroviral therapy.

Table 7.6. The predicted values of fetal BPD, HC, AC and FL at 27 and 37 weeks' gestation by timing of ART initiation.

Gestational age	Fetal BPD (mm)		Fetal HC (mm)		Fetal AC (mm)		Fetal FL (mm)	
	Pre-conception	Post-conception	Pre-conception	Post-conception	Pre-conception	Post-conception	Pre-conception	Post-conception
27 weeks (end of 2nd trimester)	68.2	70.2	244.1	249.8	213.9	220.3	48.3	49.4
37 weeks	89.8	90.7	316.4	320.1	315.6	316.8	67.8	68.5

Abbreviations: AC, abdominal circumference; ART, antiretroviral therapy; BPD, biparietal diameter; FL, femur length; HC, head circumference.

7.5 Discussion

The present study was conducted in a country that has been severely affected by the HIV epidemic [1], with >30% of HIV prevalence in pregnant women [350] and >97% of antenatal ART coverage [61]. The present findings add to the body of literature that, overall, the growth trajectories of fetal BPD, HC, AC and FL were similar between treated HIV-positive and HIV-negative women.

The present findings are corroborated by comparable HC and length data from the newborns of treated HIV-positive and HIV-negative women (Appendix 7.3: Table 7.6). The multiple linear regression adjusting for several maternal/fetal characteristics showed that treated maternal HIV infection was not associated with newborn HC or length compared with HIV-negativity (Appendix 7.3: Table 7.6).

As described in Chapter 5, most HIV-positive women in the present study received a fixed-dose combination (FDC) of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) or lamivudine (3TC) and efavirenz (EFV). Previous studies have shown an association between TDF-based regimens and decreased bone density in HIV-positive adults and children [595-597]. Another study from South Africa [598] evaluated fetal FL growth in HIV-positive pregnant women with different durations of *in utero* TDF exposure: <10, 10-24 and ≥25 weeks. Most women (93.3%) received the same ART regimen as in the present study, i.e. TDF+FTC/3TC+EFV [598]. In this study, the duration of *in utero* TDF exposure was not associated with fetal FL growth; however, a comparator group of HIV-negative women was not included, which meant that fetal FL growth trajectories could not be assessed by maternal HIV status.

Although studies comparing fetal growth patterns by maternal HIV status in a prospective longitudinal fashion have never been conducted, the effect of maternal HIV infection on neonatal anthropometry has been previously reported with inconsistent findings [599-607]. These inconsistencies in part could be attributed to study period (pre-ART versus post-ART era) and sample size. In a study conducted before the ART era [605], maternal HIV infection was associated with lower birth HC compared with HIV-negativity; however, such an association was not observed in studies conducted after the roll-out of ART [599,601-603]. Studies with relatively small sample size (n<200) [600,604,606] showed lower birth HC and length in newborns of treated HIV-positive women compared with HIV-negative women; however, these findings were not replicated in studies with a larger sample size (n>700) [601-603].

Previous studies conducted in non-HIV settings in high-income countries have shown that smoking [307], maternal folate concentrations [592], occupational exposure to several chemicals [593] and pregnancy-related complications [303,306] were associated with differences in fetal growth patterns. Maternal smoking during pregnancy reduced fetal HC and AC growth from 25 weeks' gestation onwards and FL from 18-24 weeks' gestation onwards [307]. Higher maternal folate concentrations (measured <18 weeks' gestation) were associated with faster fetal HC growth from the second to the third trimester of pregnancy [592]. Maternal occupational exposure to several chemicals (alkylphenolic compounds, pesticides and phthalates) was associated with lower fetal HC and FL growth rates [593]. In addition, reduced fetal AC growth as early as 23 weeks' gestation was observed in women with severe preeclampsia compared with

normotensive pregnant women [306]. Women with >1 day first-trimester vaginal bleeding showed decreased fetal AC late in pregnancy (34-39 weeks' gestation) compared with those without bleeding [303]. In the present study, the proportions of women who smoked during pregnancy (n=37; 6.1%), with severe preeclampsia (n=8; 1.3%) or first-trimester vaginal bleeding (n=9; 1.5%) were small. As mentioned in Chapter 5, the present study included a healthy population with low rates of alcohol and illicit drug use and acute infections; women had antenatal care (ANC) every 5±1 weeks and took folic acid and iron regularly during pregnancy (Chapter 5: Table 5.2). Furthermore, the vast majority of HIV-positive women were asymptomatic (median CD4: 451 cells/mm^3) and on an FDC of TDF+FTC/3TC+EFV (Chapter 5: Table 5.7) – representing the contemporaneous population of HIV-positive pregnant women in sub-Saharan Africa. These might have contributed to the present findings of no differences in fetal growth patterns by maternal HIV status.

Regarding timing of ART initiation, the present study has shown that, overall, the growth trajectories of fetal BPD, HC, AC and FL in HIV-positive women initiating ART pre-conception were lower than in those initiating post-conception. However, these findings should be interpreted cautiously due to the limited number of women and scans included in the present analysis (Figure 7.7).

7.5.1 Strengths and limitations

The present study has several strengths. First, to my knowledge, this is the first study comparing fetal growth patterns by maternal HIV status in a prospective longitudinal design with available information on a large number of potential

confounders. The longitudinal design allowed the present study to analyse both fetal size and growth, unlike a cross-sectional design that provides information on fetal size only. Second, ultrasound measurements were conducted in a single study site and performed by experienced, trained and dedicated ultrasonographers using a standardised protocol. Third, these measurements were performed throughout pregnancy, from 13 to 41 weeks' gestation, which enabled the present study to examine fetal growth patterns throughout pregnancy, unlike the previous studies [307,592,608-610] which only assessed fetal growth patterns in mid- and late-pregnancy. Other strengths of the present study are provided in Chapters 4 and 5.

However, several limitations are acknowledged in the present study. First, a hospital-based study with routine ANCs and iron and folic acid supplementations might have resulted in selection bias. Second, measurement error in fetal biometric parameters could still exist despite the use of a standardised protocol. Third, as there was limited information available on ART use among the HIV-positive women the present study had limited statistical power for the assessment of fetal growth patterns by timing of ART initiation, and an inability to compare fetal growth patterns by different ART regimens. Other limitations of the present study are provided in Chapters 4 and 5.

7.5.2 Implications of findings

First, the present findings highlight the importance of healthy lifestyle, routine ANC, iron and folic acid supplementations, and antenatal ART for HIV-positive women, which might have contributed to comparable fetal growth patterns

between treated HIV-positive and HIV-negative women. Second, the present sample size is sufficient for the assessment of fetal growth patterns by maternal HIV status, although a larger study could have improved precision around the point estimates by weeks of gestation. Third, larger studies are warranted to confirm whether fetal growth patterns are different according to timing of ART initiation and ART regimens. Fourth, population-based studies are needed to confirm the present findings.

Chapter 8: Final summary and recommendations

8.1 Summary

This thesis explored the effect of maternal HIV and ART on perinatal outcomes and fetal growth patterns. A detailed summary and discussion on the findings are provided in each chapter.

In Chapter 3, a systematic review and pairwise meta-analysis of observational studies was used to evaluate the risk of adverse perinatal outcomes in treated HIV-positive pregnant women. PTB, sPTB, VPTB, LBW and SGA remained significantly more common in treated HIV-positive than HIV-negative women, suggesting that ART might itself have contributed to the occurrence of adverse perinatal outcomes. This was then assessed by performing meta-analyses comparing the risk in HIV-positive women on ART versus those not on ART, which showed that antenatal ART was associated with a reduced risk of PTB, LBW and VLBW compared with no ART. The meta-analyses were then restricted to treated HIV-positive women in order to assess the effects of different ART complexity, plus class and timing of initiation, on perinatal outcomes. Regarding ART complexity, HAART has shown the greatest effect on reducing MTCT risk; however, HAART was associated with an increased risk of PTB, LBW and SGA compared with monotherapy and dual therapy. Regarding ART class, there was a weak association between PI and an increased risk of PTB compared with non PI-

based ART. For timing of ART initiation, women initiating ART pre-conception have shown a higher risk of PTB and VPTB than those initiating post-conception. Among those with post-conception initiation, first trimester initiation was not associated with any adverse perinatal outcomes compared with after first trimester initiation. Given that all studies included in the present meta-analysis were observational with inherent characteristics prone to bias, the present findings should be interpreted in the context of study methodologies.

PTB, LBW and SGA were the most frequently reported adverse perinatal outcomes among studies included in the systematic review in Chapter 3. These three perinatal outcomes, particularly LBW, have been used as a surrogate indicator of a population's infant risk for morbidity and mortality [251,252,454]. However, Chapter 4, by means of overlap analysis based on prospectively and accurately collected data, showed a substantial overlap between PTB and LBW. This suggests that it was not worthwhile to analyse them separately, and I strongly believe that LBW should be abandoned as a solitary measure in favour of combining birth weight with gestational age at birth. Poor agreement for the overlap between PTB and SGA suggests that these two perinatal outcomes are distinct: they are therefore worth distinguishing in analyses.

Chapters 5 to 7 compared the risk of adverse perinatal outcomes and fetal growth patterns in treated HIV-positive versus HIV-negative women in a "real-world" context. These were performed by analysing data from a previously conducted prospective longitudinal study in South Africa with accurately determined gestational age and birth weight and serial fetal biometric measurements. Despite

high ART coverage, good maternal health, routine ANCs and a very low MTCT rate, Chapter 5 showed a borderline significant association between treated maternal HIV infection and the composite "any adverse perinatal outcome" encompassing stillbirth, PTB, SGA or NND. Chapter 5 also showed an effect modification: treated maternal HIV infection was associated with any adverse perinatal outcome in women with ≤11 years of formal education, but not among those with >11 years. However, this effect modification became non-significant following adjustment for confounding factors.

Chapter 6 evaluated the associations between treated maternal HIV infection and specific adverse perinatal outcomes (PTB and SGA), and investigated other risk factors for PTB and SGA in both all women and HIV-negative and HIV-positive women separately. Robust analyses were performed, using both complete case and multiple imputation. The evidence in this chapter revealed that the association between treated maternal HIV infection and an increased risk of PTB was borderline significant. However, the association became significant when the analysis was stratified by marital status: treated maternal HIV infection was associated with PTB in single women, but not in married/cohabiting women. Being single was also associated with PTB in HIV-positive women, but not in HIV negative women. Other factors associated with PTB in all women were nulliparity, ≥2 previous miscarriages, history of PTB, inadequate GWG in the second trimester and gestational hypertension. In HIV-negative women, these factors included nulliparity, ≥2 previous miscarriages and history of PTB. In HIV-positive women, these factors included nutritional status, i.e. inadequate GWG in the second and third trimesters; pre-pregnancy BMI was a protective factor.

Chapter 6 also confirmed an association between treated maternal HIV infection and an approximately 60% increase in the odds of SGA. Other factors associated with SGA in all women included nulliparity, history of termination of pregnancy and inadequate GWG in the third trimester; pre-pregnancy BMI was a protective factor. In HIV-negative women, these factors included being single and ≥2 previous miscarriages; the haemoglobin level in the second trimester was a protective factor. In HIV-positive women, these factors included a history of termination of pregnancy and inadequate GWG in the third trimester; excessive GWG in the second trimester was a protective factor.

Chapter 7 is the first every analysis comparing fetal growth patterns in treated HIV-positive versus HIV-negative women. The findings in this chapter suggested that overall the growth trajectories of fetal BPD, HC, AC and FL were similar between treated HIV-positive and HIV-negative women.

A firm conclusion on the effect of timing of ART initiation on perinatal outcomes and fetal growth patterns could not be drawn in the present cohort due to limited statistical power.

8.2 Policy recommendations

Table 8.1 summarises policy recommendations that should be explored based on the findings of this thesis. These recommendations include strategies to improve the prediction, prevention, measurement and future research/surveillance of perinatal outcomes, particularly in HIV-endemic settings in LMICs. Details of these recommendations are discussed in each chapter.

Table 8.1. Recommendations to improve the prediction, prevention, measurement and future research/surveillance of perinatal outcomes in HIV-endemic settings in low and middle-income countries.

Location	Prediction	Prevention	Measurement	Future study/surveillance
All levels from community to health facility	1. Health education regarding the importance of pre-pregnancy weight and obstetric history (e.g. history of miscarriages, termination of pregnancy and PTB) as risk factors for adverse perinatal outcomes.	1. Promote pre-conception health: – Interventions for smoking, alcohol and illicit drug use and control of chronic diseases. – Weight management interventions to ensure a healthy BMI, e.g. dietary counselling, regular physical activity and healthy lifestyle. 2. Health education targeting: – The importance of early ANC, healthy pregnancy, hygiene practices and risk factors for adverse perinatal outcomes. – The importance of HIV testing and ART adherence in improving maternal health and reducing HIV comorbidity. 3. Organising ANC groups, social and emotional support, particularly for HIV-positive single women.		
Health facility and research institution	1. Risk factors assessment: extreme maternal age, being single, smoking, alcohol and illicit drug use, prenatal stress, nulliparity, histories of PTB and termination of pregnancy, ≥2 previous miscarriages, low pre-pregnancy BMI, inadequate GWG, maternal HIV infection, anaemia, gestational hypertension, ultrasonographic cervical length assessment, etc.	1. Serial antenatal ANCs (4-8 visits) beginning in the first trimester for every pregnant woman [78,611]. – Interventions promoting adequate GWG according to pre-pregnancy BMI across trimesters of pregnancy. – Interventions focused on early detection of maternal prenatal stress and stress-reduction strategies. – Early management of pre-pregnancy complications, e.g. anaemia and gestational hypertension. 2. Expansion of ART coverage for PMTCT. 3. Immediate initiation of lifelong ART in HIV-positive pregnant women, including pre-conception and first trimester.	1. Expansion of ultrasound access from primary- to tertiary-level facilities. 2. The use of first trimester ultrasound to estimate gestational age. 3. Direct standardised measurement of birth weight no later than 24h after birth. 4. The use of an international standard (instead of local reference charts) to classify birth weight for gestational age/sex. 5. Trained ultrasonographers, anthropometrists or skilled birth attendants.	1. Ongoing surveillance for the safety of *in utero* ART exposure should be a global public health priority. – The establishment of international programmatic prospective birth registries focusing on the collection of perinatal outcomes in treated HIV-positive women. – Pooled analysis or meta-analysis across surveillance cohorts particularly for rare adverse perinatal outcomes (VPTB, VSGA, stillbirth, NND). – The use of standardised definitions of adverse perinatal outcomes across studies, and the distinction

				between PTB and sPTB. 2. Ongoing surveillance for ART pharmacovigilance (tolerability, toxicity, etc.). 3. Mechanistic studies investigating underlying pathways of adverse perinatal outcomes in treated HIV-positive women. 4. Large and high-powered studies exploring the relationships between maternal HIV/ART, pre-pregnancy BMI, GWG and perinatal outcomes.
Abbreviations: ANC, antenatal care; ART, antiretroviral therapy; BMI, body mass index; GWG, gestational weight gain; HIV, human immunodeficiency virus; NND, neonatal death; PMTCT, prevention of mother-to-child transmission; PTB, preterm birth; sPTB, spontaneous preterm birth; VPTB, very preterm birth; VSGA, very small for gestational age.				

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Appendices

Appendix 1

Publication and conference abstract arising from this thesis

	Relevant thesis chapter
Original manuscript	
Santosa WB, Staines-Urias E, Tshivuila-Matala COO, Norris SA, Hemelaar J. Perinatal outcomes associated with maternal HIV and antiretroviral therapy in pregnancies with accurate gestational age in South Africa. AIDS 2019;33(10):1623-33.	5 & 6
Conference abstract	
Santosa WB, Staines-Urias E, Tshivuila-Matala COO, Norris SA, Hemelaar J. Adverse perinatal outcomes associated with maternal HIV infection and timing of antiretroviral therapy (ART) initiation in South Africa. 22nd International AIDS Conference, Amsterdam, the Netherlands, 23-27 July 2018. Abstract WEPEB121 (poster presentation).	5 & 6

Perinatal outcomes associated with maternal HIV and antiretroviral therapy in pregnancies with accurate gestational age in South Africa

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Objective: To assess the association of maternal HIV infection and antiretroviral therapy (ART) with perinatal outcomes among women with accurate pregnancy dating and birth weights.

Design: Prospective pregnancy cohort study in Soweto, South Africa.

Methods: Gestational age was estimated by first-trimester ultrasound and birth weight was measured in a standardized manner within 24 h of birth. The primary composite outcome 'adverse perinatal outcome' included preterm birth, low birth weight, small for gestational age, stillbirth and neonatal death (NND). Specific adverse perinatal outcomes were secondary outcomes. Logistic regression models adjusted for multiple confounders.

Results: Of 633 women included in the analysis, 229 (36.2%) were HIV positive and 404 (63.8%) HIV negative. Among 125 HIV-positive women who provided detailed information on HIV and ART, 96.7% had clinical stage 1 of HIV disease and 98.4% were on ART during pregnancy, mostly WHO-recommended efavirenz-based ART. Among 109 HIV-positive women with information on timing of ART initiation, 38 (34.9%) initiated ART preconception and 71 (65.1%) antenatally. No newborns were HIV positive. In univariable analysis, maternal HIV infection was associated with increased risk of the composite 'adverse perinatal outcome' [odds ratio (OR) 1.44; 95% confidence interval (CI) 1.03, 2.03], NND (OR 6.15; 95% CI 1.27, 29.88) and small for gestational age (OR 1.55; 95% CI 1.01, 2.37). After adjusting for confounders, maternal HIV infection remained associated with 'adverse perinatal outcome' (adjusted OR 1.47; 95% CI 1.01, 2.14) and NND (adjusted OR 7.82; 95% CI 1.32, 46.42). No associations with timing of ART initiation were observed.

Conclusion: Despite high ART coverage, good maternal health and very low vertical HIV transmission rate, maternal HIV infection remained associated with increased risk of adverse perinatal outcomes. Larger studies using first trimester ultrasound for pregnancy dating are needed to further assess associations with specific adverse perinatal outcomes. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: antiretroviral therapy, HIV, low birth weight, neonatal death, preterm birth, small for gestational age, stillbirth

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Introduction

In 2017, 1.5 million HIV-positive women were pregnant, of whom 91% lived in sub-Saharan Africa [1–3]. South Africa has the highest number of HIV-infected people in the world [1], and one in three pregnant women in South Africa are HIV-positive [4], of whom more than 95% now receive antenatal antiretroviral therapy (ART) [1].

Preliminary data from Botswana recently indicated that preconception dolutegravir (DTG) may be associated with a possible increased risk of neural tube defects (NTD) [5]. These findings highlight the importance of post roll-out birth outcomes surveillance, including for the current WHO-recommended first-line efavirenz (EFV)-based regimen for pregnant and breastfeeding women [6], which is currently used by the vast majority of HIV-positive women in the world, including in South Africa [7].

Untreated maternal HIV infection is associated with increased risk of adverse perinatal outcomes, including preterm birth (PTB), small for gestational age (SGA), low birth weight (LBW) and stillbirth [8]. PTB is the leading cause of neonatal and child mortality worldwide [9], and SGA and LBW are also associated with increased rates of neonatal and child morbidity and mortality [10]. Although ART in pregnancy has clear benefits for maternal health and the prevention of mother-to-child transmission (PMTCT) of HIV, studies assessing the association between ART regimens and timing of initiation of ART and adverse perinatal outcomes have yielded inconsistent results [11–18]. One possible source of this inconsistency is the use of imprecise methods to estimate gestational age and measure birth weight in most studies [11–18]. The most accurate method to estimate gestational age is an ultrasound scan in the first-trimester [19], but studies assessing pregnancy outcomes in the context of maternal HIV infection in sub-Saharan Africa almost always use less accurate methods, such as the date of the last menstrual period [11–14], symphysis-fundal height measurement [12–14], clinical assessment of the newborn [18,20] or a late ultrasound scan [12,21]. Furthermore, birth weight measurements are often poorly performed and/or reported, and often simply captured from routine obstetric records [11,12]. Inaccurate estimation of gestational age and birth weight also inevitably leads to misclassification of SGA newborns. These inaccurate methods may therefore lead to measurement error, misclassification of outcomes and biased estimates that may produce inconsistent findings regarding the effect of ART [11,12,20,22] and timing of ART initiation [12,21,23].

The aim of this study was to investigate the association of maternal HIV infection and ART with adverse perinatal outcomes among pregnant women with accurately determined gestational age and birth weight. To that end, we conducted a prospective pregnancy cohort study in Soweto, South Africa, in which gestational age was estimated by early ultrasound (<14 weeks' gestation) and birth weight measured in a standardized manner within 24 h of birth.

Methods

Study setting and design

We conducted a prospective pregnancy cohort study at Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, South Africa, the only public referral hospital in Soweto (population 1.5 million people). CHBAH implements the South African guidelines for the PMTCT. In 2013, the PMTCT guidelines recommended fixed-dose combination (FDC) of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC)/lamivudine (3TC), EFV for all HIV-positive pregnant women, irrespective of $CD4^+$ cell count [24]. In 2015, South Africa implemented option B+ [25], followed in 2016 by the 'treat all' policy, with the same first-line TDF + FTC/3TC + EFV regimen [6].

Study participants

Inclusion criteria: Black South African women, living in Soweto, aged at least 18 years, with a singleton pregnancy and spontaneous conception, and gestational age less than 14 weeks at first visit. Women were excluded if they had a multiple pregnancy, BMI more than 35 kg/m^2 (as obesity affects the accuracy of ultrasound scans) or intellectual/physical disability.

Data collection

Data were collected from 28 May 2013 to 20 July 2016. All women had a first-trimester dating ultrasound scan and women not known to be HIV-positive were routinely offered an HIV test. At enrolment, detailed information on around 200 items was collected from medical records, antenatal cards and/or interviews, encompassing sociodemographic characteristics; smoking, alcohol and illicit drug use; nutritional supplements; drug history; medical, gynaecological and obstetric history, including history of miscarriage, termination of pregnancy, PTB, LBW, stillbirth, neonatal death (NND) and pregnancy-related complications. Enroled women were seen every 5 ± 1 weeks to document any changes in health status since the previous visit. Permission was sought from HIV-positive women to collect additional information, including clinical stage of HIV disease, use of ART, ART regimens and timing of ART initiation. Detailed information on maternal HIV and ART was captured from medical records and confirmed by direct interviews. $CD4^+$ cell counts during pregnancy were obtained from the National Health Laboratory Service, South Africa, medical records and/or antenatal cards, and the first $CD4^+$ cell count measured during pregnancy was

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used. Women were followed up until delivery at which time the perinatal outcomes of interest were recorded. 98.7% of women delivered in CHBAH and 1.3% at home. Lastly, information about newborn HIV status, determined before hospital discharge, was taken from the medical records. Few variables had some missing data, but the proportion of missingness was always less than 8%, apart from $CD4^+$ cell count, for which it was less than 19%.

Measurements

A trained, dedicated ultrasonographer performed a transabdominal ultrasound scan (Philips HD-9, Philips Ultrasound, Bothell, Washington, USA) to measure the foetal crown-rump length within 3 days of enrolment. Only those women with a confirmed gestational age less than 14 weeks remained in the study. Birth weight of newborns was measured within 24 h of birth using a Seca 376 baby scale and performed independently by two trained anthropometrists. If the two anthropometrists recorded different results and the difference was more than 50 g, the measurement was repeated by each anthropometrist. If the difference was still more than 50 g, a third repetition was carried out; after the third measurement, if the difference was still more than 50 g, the average was used for our analysis. The equipment, which was calibrated twice weekly, was selected for accuracy, precision and robustness, as demonstrated in previous studies [26].

Exposure definitions

The exposures of interest included maternal HIV infection and timing of ART initiation. Among HIV-positive women, if ART was initiated before the estimated date of conception, newborns were classified as exposed to preconception ART. If ART was initiated after the estimated date of conception, newborns were classified as exposed to antenatal ART: first trimester (<15 weeks' gestation), second trimester (15–27 weeks' gestation) and third trimester (>27 weeks' gestation) initiation.

Outcome definitions

The primary outcomes were the composite outcomes 'adverse perinatal outcome' and 'severe adverse perinatal outcome'. 'Adverse perinatal outcome' included PTB (<37 weeks' gestation), LBW (<2500 g), SGA (<10th centile of the INTERGROWTH-21st Newborn Standard birth-weight-for-gestational-age/sex) [27], stillbirth (birth without any signs of life ≥24 weeks' gestation) and NND (infant death in the first 28 days of life). In addition, the 'severe adverse perinatal outcome' included very PTB (VPTB, <32 weeks' gestation), very LBW (VLBW, <1500 g), very SGA (VSGA, <3rd centile of the INTERGROWTH-21st Newborn Standard) [27], stillbirth and NND. All individual specific adverse perinatal outcomes were analysed as secondary outcomes. Congenital abnormality was defined as any abnormality observed on ultrasound examination and/or at birth.

Statistical analysis

Maternal and newborn characteristics and adverse perinatal outcomes were compared between HIV-positive and HIV-negative women and by timing of ART initiation (preconception vs. antenatal ART) among the HIV-positive group. Continuous variables were compared using two-samples *t* test or Wilcoxon–Mann–Whitney test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. For PTB, VPTB, LBW, VLBW, SGA, VSGA and NND, analyses were restricted to live newborns. Stillbirth, congenital abnormalities and composite outcomes were calculated as a proportion of all newborns. The associations between maternal HIV infection and timing of ART initiation and adverse perinatal outcomes were examined using unadjusted and adjusted logistic regression, with odds ratios (ORs) and 95% confidence intervals (95% CIs) estimated. Several confounders were defined *a priori* based on the existing literature, including maternal age, smoking, alcohol consumption, prepregnancy BMI, parity and a history of adverse perinatal outcomes. In addition, a number of confounders were identified in our sample, including maternal education, marital status and socioeconomic status. All statistical analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas, USA); *P* values were based on two-sided tests, with a value of *P* less than 0.05 considered to be statistically significant.

Ethical approval

All participants provided written consent upon enrolment. The study was approved by the University of Oxford Tropical Research Ethics Committee and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg, South Africa.

Results

A total of 680 women with singleton pregnancies and a first-trimester dating scan were recruited, of whom 633 were included in the analyses: 229 (36.2%) HIV positive and 404 (63.8%) HIV negative (Fig. 1, Table 1). The vast majority of women had accurate information on gestational age and birth weight at delivery (Fig. 1). There were 125 HIV-positive women who provided detailed information on HIV/ART. Of these, 117 (96.7%) women had WHO clinical stage 1 and 122 (98.4%) were on ART during pregnancy (Table 2): 120 received HAART, of whom 110 received FDC of TDF + FTC/3TC + EFV, five EFV-based HAART, two nevirapine (NVP)-based HAART, three lopinavir/ritonavir (LPV/r)-based HAART and two received zidovudine monotherapy. Information on timing of ART initiation was available for 109 women: 38 (34.9%)

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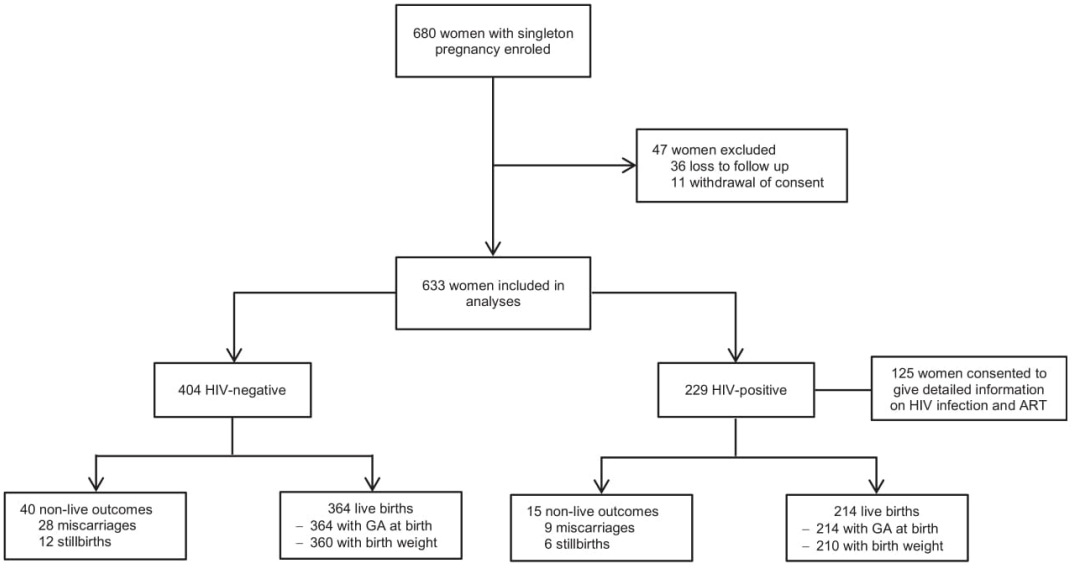

Fig. 1. Flow diagram of study participants. ART, antiretroviral therapy; GA, gestational age.

Table 1. Maternal and newborn characteristics according to maternal HIV status and timing of antiretroviral therapy initiation.

Characteristics	All women, $N=633$, *n* (%)	Women with information on HIV status, $N=633$			HIV-positive women with information on timing of ART initiation, $N=109$		
		HIV-negative, $N=404$, *n* (%)	HIV-positive, $N=229$, *n* (%)	*P* value*	Preconception ART, $N=38$, *n* (%)	Antenatal ART, $N=71$, *n* (%)	*P* value**
Maternal characteristics							
Age (years), median (IQR)	31 (26, 35)	30 (26, 34)	32 (28, 37)	<0.001	33.5 (31, 37)	30 (27, 35)	0.02
Education (years), median (IQR)	12 (11, 12)	12 (12, 12)	12 (11, 12)	0.0001	12 (11, 12)	12 (11, 12)	0.84
Married/cohabiting	245 (38.7)	167 (41.3)	78 (34.1)	0.07	17 (44.7)	29 (40.9)	0.70
Occupation[a]							
Working	227 (35.9)	149 (36.9)	78 (34.1)	0.75	14 (36.8)	23 (32.4)	0.82
Not working	86 (13.6)	55 (13.6)	31 (13.5)		4 (10.5)	10 (14.1)	
Other	320 (50.5)	200 (49.5)	120 (52.4)		20 (52.6)	38 (53.5)	
Smoked during pregnancy	40 (6.3)	24 (5.9)	16 (6.9)	0.60	2 (5.3)	5 (7)	1.00
Alcohol consumption in pregnancy	52 (8.2)	30 (7.4)	22 (9.6)	0.34	3 (7.9)	8 (11.3)	0.74
Socioeconomic status[b]							
Low	121 (19.1)	80 (19.8)	41 (17.9)	0.02	6 (15.8)	12 (16.9)	0.98
Middle	277 (43.8)	160 (39.6)	117 (51.1)		18 (47.4)	34 (47.9)	
High	235 (37.1)	164 (40.6)	71 (31)		14 (36.8)	25 (35.2)	
Prepregnancy BMI							
Underweight (<18.50 kg/m^2)	10 (1.6)	8 (1.9)	2 (0.9)	0.63	0	0	0.12
Normal (18.50–24.99 kg/m^2)	224 (35.4)	138 (34.2)	86 (37.5)		18 (47.4)	20 (28.2)	
Overweight (25.0–29.99 kg/m^2)	234 (36.9)	153 (37.9)	81 (35.4)		13 (34.2)	30 (42.2)	
Obese (≥30 kg/m^2)	165 (26.1)	105 (26)	60 (26.2)		7 (18.4)	21 (29.6)	
Nulliparity	102 (17.2)	75 (20)	27 (12.3)	0.02	2 (5.4)	12 (17.4)	0.08
History of stillbirth	61 (10.3)	44 (11.8)	17 (7.8)	0.13	3 (8.1)	1 (1.5)	0.12
History of termination of pregnancy	39 (6.2)	22 (5.5)	17 (7.4)	0.32	3 (7.9)	7 (9.9)	1.00
History of preterm birth	119 (20)	77 (20.5)	42 (19.2)	0.69	8 (21.6)	12 (17.4)	0.60
History of low birth weight	91 (15.4)	64 (17.2)	27 (12.4)	0.12	4 (10.8)	8 (11.6)	1.00
History of neonatal death	38 (6.4)	23 (6.1)	15 (6.9)	0.73	1 (2.7)	2 (2.9)	1.00
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (11, 13)	0.41	11 (10, 13)	12 (10, 13)	0.66
Caesarean section	340 (53.7)	214 (53)	126 (55)	0.62	25 (65.8)	47 (66.2)	0.97
Newborn characteristics							
Female newborn	292 (47.3)	189 (48.5)	103 (45.4)	0.46	23 (60.5)	26 (36.6)	0.02
Gestational age at delivery (weeks), median (IQR)	38.5 (37, 40)	39 (37, 40)	38 (37, 39)	0.24	38 (37, 39)	39 (37, 39)	0.30
Birth weight (g), median (IQR)	2990 (2600, 3260)	2995 (2652.5, 3265)	2962.5 (2540, 3255)	0.25	2940 (2495, 3210)	3070 (2595, 3305)	0.30
Birth-weight-for-gestational-age centile, median (IQR)	33.6 (13.4, 63.1)	34.4 (15.5, 64.2)	31.1 (11.3, 61.2)	0.29	34.9 (8.0, 53.8)	33.9 (11.4, 64.8)	0.69
Congenital abnormalities	11 (1.7)	7 (1.7)	4 (1.8)	1.00	2 (5.3)	2 (2.8)	0.61
HIV positive	0	0	0	–	0	0	–

ART, antiretroviral therapy; IQR, interquartile range.
[a]Working: any paid job; not working: housework and student; other: redundancy or unemployed.
[b]Socioeconomic status was determined using asset-based measures at household level categorized as low, middle and high using a wealth index score generated from multiple correspondence analysis.
*P value from chi-square test, Fisher's exact test or Wilcoxon–Mann–Whitney test, as appropriate, for comparisons between HIV-positive and HIV-negative women.
**P value from chi-square test, Fisher's exact test or Wilcoxon–Mann–Whitney test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

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Table 2. Maternal HIV-related characteristics.

Characteristics	HIV-positive women with information on HIV and ART, $N=125$, *n* (%)	HIV-positive women with information on timing of ART initiation, $N=109$		
		Preconception ART, $N=38$, *n* (%)	Antenatal ART, $N=71$, *n* (%)	*P* value*
Clinical HIV stage (WHO)				
Stage 1	117 (96.7)	35 (97.2)	66 (95.7)	0.79
Stage 2	2 (1.7)	0	2 (2.9)	
Stage 3	2 (1.7)	1 (2.8)	1 (1.4)	
Stage 4 (AIDS)	0	0	0	
Received ART during pregnancy	122 (98.4)			
ART regimen				
Zidovudine monotherapy	2 (1.6)	0	2 (2.8)	0.54
HAART	120 (98.4)	38 (100)	69 (97.2)	
$CD4^+$ cell count during pregnancy				
<200 cells/μl	9 (8.3)	1 (3.2)	8 (12.1)	0.03
200–349 cells/μl	20 (18.5)	5 (16.1)	13 (19.7)	
350–499 cells/μl	43 (39.8)	19 (61.3)	20 (30.3)	
≥500 cells/μl	36 (33.3)	6 (19.4)	25 (37.9)	

ART, antiretroviral therapy.
**P* value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

initiated ART preconception and 71 (65.1%) initiated during pregnancy (58 during the first trimester, 12 during the second/third trimester and one unknown trimester) (Table 2 and Supplementary Table 1, http://links.lww.com/QAD/B471).

The comparison of maternal characteristics by HIV status and timing of ART initiation are presented in Table 1. HIV-positive women were significantly older, less educated, more likely to be parous and had a different distribution of socioeconomic status compared with HIV-negative women. Women receiving preconception ART were significantly older than those on antenatal ART (Table 1), and women on antenatal ART more commonly had low or high $CD4^+$ cell counts (Table 2). Among women who initiated ART during pregnancy, maternal characteristics were comparable between those who initiated ART during the first trimester and second/third trimester (Supplementary Table 1, http://links.lww.com/QAD/B471).

Adverse perinatal outcomes among all women

Among all 633 women included in the analysis, 210 (33.2%) had an adverse perinatal outcome, and 75 (11.9%) a severe adverse perinatal outcome. Among the 578 live births there were 99 (17.1%) PTB and 26 (4.5%) VPTB; 114 (20%) LBW and 21 (3.7%) VLBW; and 106 (18.7%) SGA and 30 (5.3%) VSGA (Table 3, Fig. 2).

Table 3. Adverse perinatal outcomes according to maternal HIV status and timing of antiretroviral therapy initiation.

Adverse perinatal outcomes	All women, $N=633$, *n* (%)	Women with information on HIV status, $N=633$			HIV-positive women with information on timing of ART initiation, $N=109$		
		HIV-negative, $N=404$, *n* (%)	HIV-positive, $N=229$, *n* (%)	*P* value*	Preconception ART, $N=38$, *n* (%)	Antenatal ART, $N=71$, *n* (%)	*P* value**
Adverse perinatal outcome[a]	210 (33.2)	122 (30.2)	88 (38.4)	0.04	16 (42.1)	23 (32.4)	0.31
Severe adverse perinatal outcome[b]	75 (11.9)	44 (10.9)	31 (13.5)	0.32	4 (10.5)	7 (9.9)	1.00
PTB (<37 weeks)	99 (17.1)	56 (15.4)	43 (20.1)	0.15	9 (24.3)	10 (14.7)	0.22
VPTB (<32 weeks)	26 (4.5)	15 (4.1)	11 (5.1)	0.57	2 (5.4)	1 (1.5)	0.28
LBW (<2500 g)	114 (20)	67 (18.6)	47 (22.4)	0.28	10 (27)	11 (16.7)	0.21
VLBW (<1500 g)	21 (3.7)	13 (3.6)	8 (3.8)	0.90	2 (5.4)	1 (1.5)	0.29
SGA (<10th centile)	106 (18.7)	58 (16.2)	48 (23)	0.04	10 (27)	13 (19.7)	0.39
VSGA (<3rd centile)	30 (5.3)	17 (4.7)	13 (6.2)	0.45	3 (8.1)	3 (4.6)	0.66
Stillbirth	18 (2.8)	12 (3)	6 (2.6)	0.80	0	1 (1.4)	1.00
NND	9 (1.6)	2 (0.6)	7 (3.3)	0.02	1 (2.7)	2 (2.9)	1.00

ART, antiretroviral therapy; LBW, low birth weight; NND, neonatal death; PTB, preterm birth; SGA, small for gestational age; VLBW, very low birth weight; VPTB, very preterm birth; VSGA, very small for gestational age.
[a]Adverse perinatal outcome includes PTB, LBW, SGA, stillbirth and NND.
[b]Severe adverse perinatal outcome includes VPTB, VLBW, VSGA, stillbirth and NND.
**P* value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive and HIV-negative women.
***P* value from chi-square test or Fisher's exact test, as appropriate, for comparisons between HIV-positive women with preconception and antenatal ART.

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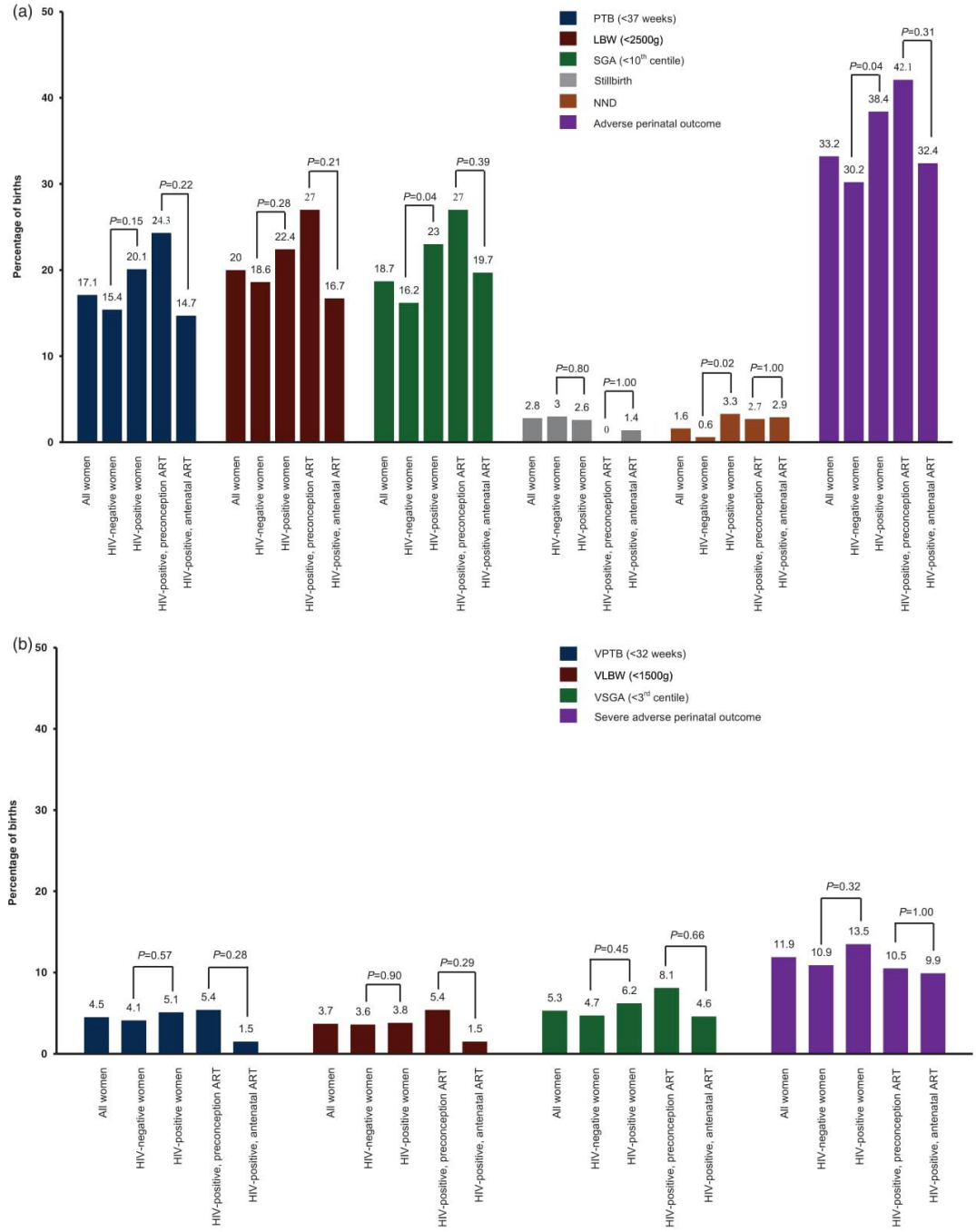

Fig. 2. Incidence of adverse perinatal outcomes according to maternal HIV status and timing of ART initiation. (a) Preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA), stillbirth, neonatal death (NND) and adverse perinatal outcome (composite outcome of preterm birth, low birth weight, small for gestational age, stillbirth and neonatal death). (b) Very preterm birth (VPTB), very low birth weight (VLBW), very small for gestational age (VSGA) and severe adverse perinatal outcome (composite outcome of very preterm birth, very low birth weight, very small for gestational age, stillbirth and neonatal death). *P* values for comparisons are indicated on top of the bars (Table 3). ART, antiretroviral therapy.

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Table 4. Unadjusted and adjusted associations[a] between maternal HIV status and timing of antiretroviral therapy initiation and adverse perinatal outcomes.

	Women with information on HIV status, $N = 633$		HIV-positive women with information on timing of ART initiation, $N = 109$	
Adverse perinatal outcomes	OR (95% CI) for HIV-positive (Ref: HIV-negative)	*P* value*	OR (95% CI) for preconception ART (Ref: antenatal ART)	*P* value**
Adverse perinatal outcome[b]				
Unadjusted	1.44 (1.03, 2.03)	0.04	1.52 (0.67, 3.42)	0.32
Adjusted	1.47 (1.01, 2.14)	0.04	1.17 (0.45, 3.08)	0.75
Severe adverse perinatal outcome[c]				
Unadjusted	1.28 (0.78, 2.09)	0.32	1.08 (0.29, 3.93)	0.91
Adjusted	1.38 (0.81, 2.36)	0.24	1.56 (0.35, 6.84)	0.56
PTB (<37 weeks)				
Unadjusted	1.38 (0.89, 2.15)	0.15	1.86 (0.68, 5.10)	0.22
Adjusted	1.40 (0.86, 2.26)	0.17	2.27 (0.70, 7.32)	0.17
VPTB (<32 weeks)				
Unadjusted	1.26 (0.57, 2.80)	0.57	3.83 (0.34, 43.71)	0.28
Adjusted	1.26 (0.53, 3.02)	0.60	–	–
LBW (<2500 g)				
Unadjusted	1.26 (0.83, 1.92)	0.28	1.85 (0.70, 4.90)	0.21
Adjusted	1.15 (0.73, 1.82)	0.55	1.92 (0.60, 6.15)	0.27
VLBW (<1500 g)				
Unadjusted	1.06 (0.43, 2.59)	0.90	3.71 (0.33, 42.42)	0.29
Adjusted	1.14 (0.43, 3.04)	0.79	–	–
SGA (<10th centile)				
Unadjusted	1.55 (1.01, 2.37)	0.04	1.51 (0.59, 3.89)	0.39
Adjusted	1.45 (0.91, 2.33)	0.12	1.09 (0.32, 3.76)	0.89
VSGA (<3rd centile)				
Unadjusted	1.33 (0.63, 2.81)	0.45	1.85 (0.35, 9.68)	0.47
Adjusted	1.50 (0.66, 3.44)	0.34	3.23 (0.38, 27.88)	0.29
Stillbirth				
Unadjusted	0.88 (0.33, 2.37)	0.80	–	–
Adjusted	0.77 (0.24, 2.41)	0.65	–	–
NND				
Unadjusted	6.15 (1.27, 29.88)	0.02	0.92 (0.08, 10.46)	0.94
Adjusted	7.82 (1.32, 46.42)	0.02	–	–

95% CI, 95% confidence interval; ART, antiretroviral therapy; LBW, low birth weight; NND, neonatal death; OR, odds ratio; PTB, preterm birth; Ref, reference; SGA, small for gestational age; VLBW, very low birth weight; VPTB, very preterm birth; VSGA, very small for gestational age.
[a]Adjusted for maternal age, education, marital status, smoking, alcohol consumption, socioeconomic status, prepregnancy BMI, parity, history of stillbirth, history of preterm birth, history of low birth weight and history of neonatal death.
[b]Adverse perinatal outcome includes PTB, LBW, SGA, stillbirth and NND.
[c]Severe adverse perinatal outcome includes VPTB, VLBW, VSGA, stillbirth and NND.
**P* value from unadjusted and adjusted logistic regression, as appropriate, for the associations between maternal HIV infection and adverse perinatal outcomes.
***P* value from unadjusted and adjusted logistic regression, as appropriate, for the associations between timing of ART initiation and adverse perinatal outcomes.

Adverse perinatal outcomes by maternal HIV status

The incidence of specific adverse perinatal outcomes, with the exception of stillbirth, was higher in HIV-positive than HIV-negative women (Table 3, Fig. 2). Maternal HIV infection was associated with a significant increase in the risk of the composite 'adverse perinatal outcome' (38.4 vs. 30.2%; OR 1.44; 95% CI 1.03, 2.03), NND (3.3 vs. 0.6%; OR 6.15; 95% CI 1.27, 29.88) and SGA (23 vs. 16.2%; OR 1.55; 95% CI 1.01, 2.37). After adjustment for maternal age, education, marital status, smoking, alcohol consumption, socioeconomic status, prepregnancy BMI, parity and a history of adverse perinatal outcomes, maternal HIV infection remained associated with the composite 'adverse perinatal outcome' [adjusted OR (AOR) 1.47; 95% CI 1.01, 2.14] and NND (AOR 7.82; 95% CI 1.32, 46.42), but not SGA (AOR 1.45; 95% CI 0.91, 2.33) (Table 4). There were no cases of mother-to-child transmission of HIV identified at hospital discharge (Table 1).

Adverse perinatal outcomes by timing of antiretroviral therapy initiation

Among HIV-positive women, the incidences of composite and specific adverse perinatal outcomes were higher among women who initiated ART preconception than those who initiated ART antenatally, except for stillbirth and NND (Table 3, Fig. 2). However, none of the adverse perinatal outcomes were significantly associated with timing of ART initiation in either the unadjusted or adjusted models (Table 4). The inclusion of $CD4^+$ cell count during pregnancy in the models did not change these associations (data not shown). Due to the limited number of outcome events, we could not perform

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adjusted analyses of the associations between timing of ART initiation and VPTB, VLBW, stillbirth and NND.

Among HIV-positive women who initiated ART antenatally, the incidences of all adverse perinatal outcomes assessed were higher among women who initiated ART in the first trimester compared with second/third trimester (Supplementary Table 2, http://links.lww.com/QAD/B471). However, trimester of ART initiation was not significantly associated with the composite 'adverse perinatal outcome', or PTB, LBW and SGA in both univariable and multivariable analyses. Adjusted modes could not be fitted for VPTB, VLBW, VSGA, stillbirth and NND due to the limited number of outcome events (Supplementary Table 3, http://links.lww.com/QAD/B471).

Congenital abnormalities

Overall, 11 (1.7%) of 633 births had congenital abnormalities (Table 1): hydronephrosis, hypotrophy of cerebrum, dilated ventricles, gastroschisis, narrow chest and disorganized pelvis, spina bifida (born to an HIV-positive woman with first-trimester initiation of ART), malformation of lower limbs, club foot, polydactyly, ventricular septal defect and gross congenital malformation.

Discussion

The benefits of ART during pregnancy in reducing new paediatric HIV infections and improving maternal health are indisputable. In this study, there were no newborns diagnosed with HIV and, among the subgroup of HIV-positive women with ART information, 96.7% were asymptomatic of HIV disease (Tables 1 and 2). However, our findings showed that HIV-positive women still have significantly higher overall rates of adverse perinatal outcomes compared with HIV-negative women (38.4 vs. 30.2%, $P = 0.04$) (Table 3, Fig. 2), despite high ART coverage with WHO-recommended first-line TDF + FTC/3TC + EFV. On the other hand, treated maternal HIV infection was not significantly associated with PTB, which is in agreement with an existing study [20], but in contrast to other studies [11,12,17,28]. The lack of association between maternal HIV infection and LBW in our study is similar to another study [12], but not others [11,17]. Our finding of nonsignificant association between maternal HIV infection and SGA is consistent with two studies [11,12], but in contrast to another study [17]. The lack of significant associations between maternal HIV infection and a number of specific perinatal outcomes could be due to limited statistical power to detect modest effects because of the sample size and the number of events for some outcomes. Our study, including over 630 women with an HIV prevalence of 36% and a composite outcome prevalence of 30%, was adequately powered to detect ORs at least 1.5. For analyses including a smaller subset of patients (such as the HIV-positive women with ART initiation information) or a less common outcome (like some of the rare perinatal outcomes), there was less statistical power, as evidenced by the wider CIs of the ORs for these comparisons. Imprecise and varying methods to determine gestational age and birth weight might also contribute to inconsistent results between studies.

HIV-positive women in our study had a higher incidence of NND (3.3%) compared with women treated with EFV-based ART in Botswana (1.9%) [29]. The rate of NND was also higher than that reported for HIV-positive women on DTG-based ART (1.2%) [14] and NVP-based ART (1.9%) [13], but similar to women treated with LPV/r-based ART (2.8%) [13]. In contrast, we found a low rate of NND (0.6%) in the HIV-negative women, despite the high overall rate of adverse perinatal outcomes, such as PTB, SGA and LBW. A recent study from South Africa reported that the most common causes of early NND are PTB-related complications (49.2%) [30]. Of the nine NNDs that occurred in our study, eight infants were born less than 28 weeks' gestation (six born to HIV-positive and two born to HIV-negative women) and one at 35 weeks' gestation (to an HIV-positive woman), and all nine infants had a birth weight less than 1500 g and were admitted to the ICU. It is likely that maternal HIV infection significantly increased the risk of NND in our study because of the higher incidence of extremely PTB.

As well as the composition of the ART regimen, the timing of initiation of ART has been reported to correlate with adverse perinatal outcomes, with preconception initiation being associated with higher rates of adverse perinatal outcomes than antenatal initiation [13,16]. In our study, the overall rate of adverse perinatal outcomes among the 38 women known to have initiated ART preconception (42.1%) was higher than that reported in women who received EFV-based preconception ART in a study in Botswana (36.7%) [29]; however, the rate of adverse perinatal outcome was lower among the 71 women who initiated ART antenatally (32.4%) in our study compared with EFV-based antenatal ART in Botswana (35.0%) [29]. Despite the 10% difference (42.1 vs. 32.4%) in adverse perinatal outcome rates in the preconception and antenatal initiation groups in our study, the association between timing of ART initiation and adverse perinatal outcome was NS. This could be due to inadequate statistical power, given the limited number of women with available ART information, and the small number of outcome events (as judged by the wide CIs for the ORs for this subgroup). Furthermore, the limited statistical power could be a reason why this study was unable to detect an increased risk of PTB among women who initiated ART preconception than those who initiated antenatally. This finding was in contrast to a meta-analysis by Uthman *et al.* [16] which has shown a 40% increase in the risk of PTB among women with

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preconception initiation of ART in low-income and middle-income countries. Regarding the nonsignificant associations between timing of ART initiation and LBW and SGA, our findings were similar to those reported by another South African study [12].

Questions have been raised as to whether reported associations between timing of ART initiation and perinatal outcomes could be due to selection bias, as the women in the antenatal initiation group, who often start ART late in pregnancy in African settings [18], might not have the same opportunity as women on preconception ART to experience adverse events within a study, as these may have occurred prior to possible enrolment, for example PTB [31]. Although in our study all women were recruited prospectively very early in pregnancy, thereby minimizing the aforementioned selection bias, our study had limited ability to draw firm conclusions regarding ART timing of initiation, due to limited power.

The rates of congenital abnormalities in our study were similar between HIV-positive and HIV-negative women (1.8 vs. 1.7%, $P = 1.00$), despite most HIV-positive women commencing ART either preconception or in the first trimester (Supplementary Table 1, http://links.lww.com/QAD/B471). This finding is similar to the results from a Ugandan study (in which 77% of HIV-positive women received EFV-based HAART) [32] and the Antiretroviral Pregnancy Registry [33].

Our study has several strengths. This is, to our knowledge, the first prospective pregnancy cohort study conducted in sub-Saharan Africa investigating adverse perinatal outcomes in HIV-positive women in which all women had a first-trimester ultrasound scan. Ultrasound in the first trimester is the most accurate method to date a pregnancy [19] which minimizes misclassification of gestational age at birth. All women in our study were recruited at less than 14 weeks' gestation and prospectively followed up which enabled us to capture adverse perinatal outcomes from an early gestational age. Pregnant women commonly present late for antenatal care in sub-Saharan Africa [18], which not only hampers accurate gestational age assessment but also leads to an underestimation of adverse perinatal outcomes in prospective studies, as adverse outcomes may occur prior to enrolment. Furthermore, the measurement of birth weight was directly performed by trained anthropometrists using standardized techniques and instruments, and was conducted within 24 h of birth, which minimized random measurement error and misclassification of birth weight. We used the INTERGROWTH-21st Newborn Standards [27] to determine which newborns were SGA, thereby enabling international comparison with other studies using the same standard [12,13,17,29]. Extrapolating from the subgroup with information on ART, the population studied had high ART coverage and most HIV-positive women initiated EFV-based ART preconception or in the first trimester. This enabled assessment of adverse perinatal outcomes in HIV-positive women on first-line WHO-recommended ART, as implemented in most affected countries in the world [7]. A large number (>200) of variables relating to socioeconomic, medical and obstetric risk factors were collected through direct measurements, interviews, medical records and antenatal cards. Data quality was very high, with a very small number of missing data; for example, only eight (1.4%) of 578 live newborns had missing birth weight data, which is a great achievement in a very busy hospital in a low resource setting. Logistic regression models were used to adjust for multiple confounders, identified either *a priori* or based on our data, including detailed information on adverse perinatal outcomes in previous pregnancies.

Nevertheless, this study has some limitations. First, we were unable to demonstrate causal inference due to the nature of the observational study (potential unmeasured confounding). Second, the rarity of events found in several adverse perinatal outcomes (including VPTB, VLBW, VSGA, stillbirth and NND) limited our ability to perform adjusted analyses of the association between these outcomes and timing of ART initiation. Third, limited information on timing of ART initiation among HIV-positive women, due to limited consent given, resulted in limited statistical power for the association between timing of ART initiation and adverse perinatal outcomes. Fourth, it may be difficult to generalize our findings to other settings with different populations and risk factors.

It is crucial to optimize ART regimens during pregnancy to further improve perinatal outcomes and associated neonatal and child morbidity and mortality, as well as eliminate HIV transmission and improve maternal health. As of the end of 2017, almost 60 low- and middle-income countries have incorporated or are planning to include DTG in their national guidelines, as a preferred first-line drug. However, clinical evidence of DTG safety in pregnant women is still very limited [34]. A study from Botswana recently reported that DTG-based ART had similar adverse perinatal outcomes to EFV-based ART among women who initiated ART antenatally, although these were still higher than their HIV-negative counterparts [14]. In addition, an interim analysis of the same cohort in Botswana indicated a potential association between DTG-based ART initiated preconception and an increased risk of NTD [5]. Therefore, ongoing surveillance of pregnancy outcomes among HIV-positive women on ART remains crucial.

Despite high coverage with WHO-recommended EFV-based ART, good maternal health and a very low rate of mother-to-child HIV transmission, maternal HIV infection remains associated with an increased risk of adverse perinatal outcomes in South Africa. More, larger studies,

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including randomized controlled trials, are needed to determine the optimal ART regimen and timing of ART initiation in pregnant women. To improve the reliability and comparability of future studies, they should recruit women at an early gestational age (<14 weeks); use first-trimester ultrasound to estimate gestational age accurately; measure birth weight in a standardized manner within 24 h of birth; and use the INTERGROWTH-21st Newborn Standard of birth-weight-for-gestational-age/sex to classify SGA.

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W.B.S. conducted the data analysis, including the statistical analysis, interpreted the data, made the tables and figures and wrote the first draft of the article. E.S.-U. advised on the statistical analysis. C.O.O.T.-M. codesigned the HIV/ART data collection sheet, trained the study nurses to collect HIV/ART data and coordinated part of the study locally. S.A.N. coordinated the study at the study site. J.H. conceived, designed and coordinated the study, codesigned the HIV/ART data collection sheet, designed the analysis plan, interpreted the data and wrote the article. All authors read and approved the final version of the article.

Conflicts of interest

There are no conflicts of interest.

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Adverse perinatal outcomes associated with maternal HIV infection and timing of antiretroviral therapy (ART) initiation in South Africa

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Background

Untreated maternal HIV infection has been shown to be associated with an increased risk of preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA) and stillbirth.[1] The associations between adverse perinatal outcomes and treated maternal HIV infection and timing of ART initiation have been widely investigated, however with inconsistent findings.

In most studies:
- Gestational age was estimated using imprecise methods:
  - Last menstrual period (LMP)[2,3]
  - Symphyseal-fundal height (SFH)[2]
  - Clinical assessment of newborns (Ballard,[4] Finnström[5,6] and Dubowitz[7])
  - Late ultrasound[5,8]

Birth weight was captured from obstetric records without taking direct measurements[2]

The use of imprecise methods may lead to random measurement error, misclassification of adverse perinatal outcomes, biased estimates and inconsistent findings.

We conducted a prospective pregnancy cohort study in which gestational age was accurately estimated using a first-trimester ultrasound and birth weight was directly measured.

Aims

The study was aimed at investigating the associations between adverse perinatal outcomes and (1) treated maternal HIV infection; (2) timing of ART initiation (preconception vs antenatal) among pregnant women in South Africa.

Methods (1)

Study setting:
This prospective pregnancy cohort study was conducted at the Chris Hani Baragwanath Hospital (CHBH), Soweto, South Africa.

Study period:
May 2013 to June 2016, after the availability of fixed-dose combination (FDC) of triple antiretrovirals.

Inclusion criteria:
- Women aged ≥18 years
- Singleton pregnancy
- Spontaneous conception
- Gestational age <14 weeks
- Black South African
- Living in Soweto

Exclusion criteria:
- Multiple pregnancy
- BMI >35 kg/m²
- Intellectual and physical disability

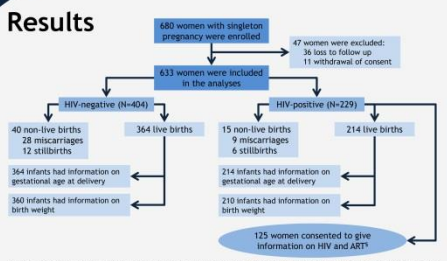
Outcome measurements:
- Gestational age (GA): first-trimester (<14 weeks) ultrasound measurement of the crown-rump length (CRL)
- Birth weight measurement was conducted as soon as possible, <24 hours after delivery

Follow-up*

- **Recruitment**: GA: <14 weeks; Information on maternal characteristics was collected
- **Follow-up 1**: GA: ±20 weeks; Current pregnancy conditions
- **Follow-up 2**: GA: ±26 weeks; Current pregnancy conditions
- **Follow-up 3**: GA: ±32 weeks; Current pregnancy conditions
- **Follow-up 4**: GA: ±38 weeks; Current pregnancy conditions
- **Delivery**: Adverse perinatal outcomes were recorded

*At any of the follow-up visits or delivery, HIV-positive women were consented to give information related to HIV and ART.

Results



§Most women (90.2%) received FDC of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC)/lamivudine (3TC) and efavirenz (EFV)

Figure 1. Flow diagram of study participants

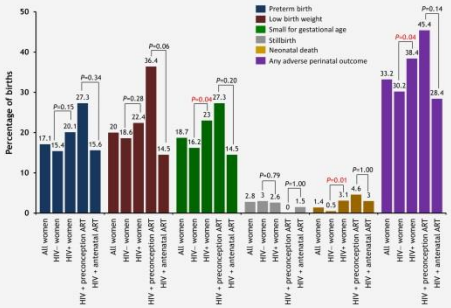


Figure 2. The incidence of PTB, LBW, SGA, stillbirth, neonatal death and any adverse perinatal outcome according to maternal HIV status and timing of ART initiation[¶]

¶P values were obtained from the chi-square or Fisher's exact test, as appropriate.

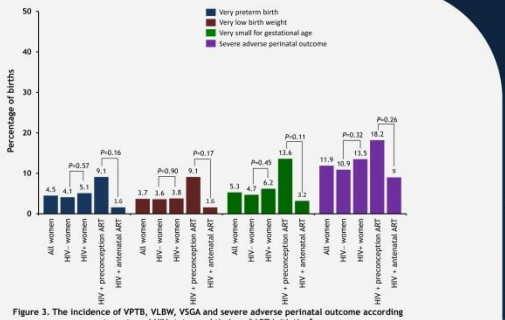


Figure 3. The incidence of VPTB, VLBW, VSGA and severe adverse perinatal outcome according to maternal HIV status and timing of ART initiation[¶]

¶P values were obtained from the chi-square or Fisher's exact test, as appropriate.

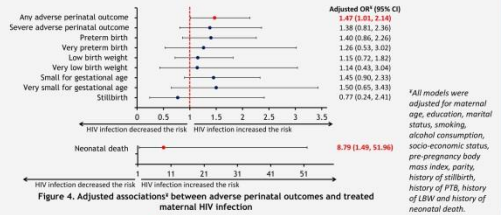


Figure 4. Adjusted associations‡ between adverse perinatal outcomes and treated maternal HIV infection

‡All models were adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of stillbirth, history of PTB, history of LBW and history of neonatal death.

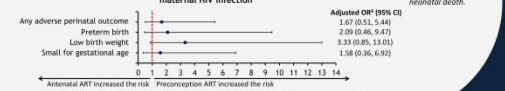


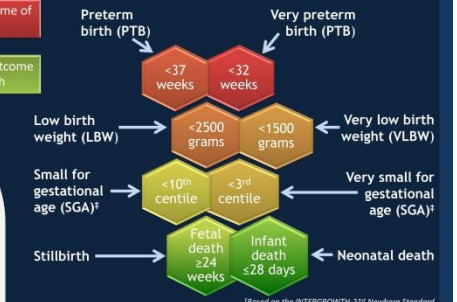
Figure 5. Adjusted associations‡ between adverse perinatal outcomes and timing of ART initiation

Methods (2)

Primary outcomes

- **Any adverse perinatal outcome:** composite outcome of PTB, LBW, SGA, stillbirth and neonatal death
- **Severe adverse perinatal outcome:** composite outcome of VPTB, VLBW, VSGA, stillbirth and neonatal death

Secondary outcomes



‡Based on the INTERGROWTH-21st Newborn Standard

Statistical analysis

- The associations between adverse perinatal outcomes and treated maternal HIV infection and timing of ART initiation were examined using logistic regression adjusted for several confounders, reported as odd ratios (OR) and their 95% confidence intervals (CI).
- For PTB, VPTB, LBW, VLBW, SGA and VSGA, analyses were restricted to live newborns.

Conclusion

- Despite the availability of FDC of triple antiretrovirals, all adverse perinatal outcomes (except stillbirth) were increased in HIV-positive (compared to HIV-negative) women and with preconception (compared to antenatal) initiation of ART, but only any adverse perinatal outcome and neonatal death were significantly associated with treated maternal HIV infection after adjusting for confounders.
- HIV-positive women should receive counselling regarding the risk of adverse perinatal outcomes, in addition to mother-to-child-transmission of HIV.
- Larger studies are needed to investigate the association between adverse perinatal outcomes and timing of ART initiation.

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Chapter 2: List of appendices

Appendix 2.1 : Key historical events of HIV/AIDS.

Appendix 2.2 : HIV-1 molecular structure and transmission.

Appendix 2.3 : Antiretroviral therapy.

Appendix 2.4 : Phenotypic classification of preterm birth.

Appendix 2.1

Key historical events of HIV/AIDS.

Table 2.1. Key historical events of HIV/AIDS between 1981 and 2019.

Year	Key historical event
1981	– A new disease of severe immunodeficiency was recognised among gay men in the USA. The disease was characterised by unusual opportunistic infections (e.g. Pneumocystis pneumonia) and malignancies (e.g. Kaposi's sarcoma) [1-3]. – By the end of the year, 337 cases were reported in the USA: 321 adults/adolescents and 16 children <13 years, 130 of them died [4].
1982	– The Centers for Disease Control and Prevention (CDC) issued the first article suggesting a potential connection between a sexually-transmitted agent and the outbreaks of Kaposi's sarcoma, Pneumocystis pneumonia and other opportunistic infections [5]. – Three immunosuppression cases were also reported in three heterosexual patients with haemophilia A [6]. – CDC used the term “acquired immunodeficiency syndrome” (AIDS) for the first time [7]. – A transfusion-associated AIDS was reported in a 20-month-old infant [8]. Other 22 cases of unexplained immunodeficiency and opportunistic infections suggestive of AIDS were also reported in infants [9]. – AIDS cases were also reported in several European countries [10-12]. In Uganda, a new locally known “slim disease” was reported with major symptoms: weight loss and diarrhea [13]. – AIDS organisations were established, including the San Francisco AIDS Foundation (USA) and the Terrence Higgins Trust (UK) [4].
1983	– Two women developed immunodeficiency during a close relationship (including repeated sexual contact) with men who had AIDS – suggesting that the disease could be transmitted via heterosexual intercourse [14]. CDC suggested that AIDS was an infectious disease transmitted sexually or through exposure to blood or blood products [15]. The possibility of vertical transmission from an affected mother to her infant before, during, or shortly after birth was also suggested [16]. – A new retrovirus called lymphadenopathy-associated virus (LAV) was discovered; LAV could be the cause of AIDS [17]. – The World Health Organization (WHO) held the first AIDS meeting and started international surveillance [18].
1984	– A retrovirus called human T-cell lymphotropic virus type-III (HTLV-III) was discovered, and this virus was identical to LAV [19].
1985	– The first commercial blood test to detect antibodies to the virus was licensed by the US Food and Drug Administration (FDA) [20]. – The first international AIDS conference was held in Atlanta, Georgia [4]. – To prevent mother-to-child transmission (MTCT), CDC recommended women to 1) delay pregnancy until more is known about perinatal transmission and 2) avoid breastfeeding [21]. – By the end of the year, every region in the world had reported at least one AIDS case [4].
1986	– The virus of AIDS was officially called human immunodeficiency virus (HIV) [4].

Table 2.1. Key historical events of HIV/AIDS between 1981 and 2019 (*continued from previous page*).

Year	Key historical event
1987	– FDA approved the first antiretroviral (ARV) drug for HIV (zidovudine) [4]. Guidelines on the prevention of HIV transmission in health care settings were published [22].
1988	– The 1st December was announced as the world AIDS day [4].
1989	– CDC issued the first guidelines for preventing Pneumocystis pneumonia – the main cause of illness and death for AIDS patients [23].
1990	– FDA approved the use of zidovudine for AIDS treatment in children [4].
1991	– Red ribbon was launched as an international symbol of AIDS awareness [4].
1992	– AIDS became the first leading cause of death for men aged 25–44 years in the USA [24]. – FDA approved a 10-minute diagnostic test kit for HIV-1 [4].
1993	– Research on women and HIV/AIDS was begun in the USA [4]. – CDC used CD4 <200 to define AIDS, and added pulmonary tuberculosis, recurrent pneumonia and invasive cervical cancer to the list of clinical indicators of AIDS [25]. – An estimated 14 million HIV infections and 2.5 million AIDS cases were reported globally [26].
1994	– AIDS became the first leading cause of death for people aged 25–44 years in the USA [4]. – The first randomised controlled trial by the Pediatric AIDS Clinical Trials Group showed that antenatal zidovudine reduced the risk of MTCT by approximately 67.5% [27]. – CDC recommended the use of Zidovudine to reduce the risk of perinatal HIV transmission [28].
1995	– FDA approved the first protease inhibitor – the beginning of highly active antiretroviral therapy (HAART) era [4].
1996	– The 11th International AIDS Conference highlighted the effectiveness of HAART [4]. – AIDS was no longer the first leading cause of death among people aged 25-44 years in the USA [4]. – The Joint United Nations Programme on HIV/AIDS (UNAIDS) was established [29]. – FDA approved a viral load test and the first non-nucleoside reverse transcriptase inhibitor (NNRTI) drug – nevirapine [4].
1997	– The use of HAART was associated with a 47% reduction in AIDS-related deaths in the USA. – FDA approved combivir, a combination of zidovudine and lamivudine. – Approximately 30 million people worldwide were HIV-positive [4].
1998	– CDC issued the first national treatment guidelines on the use of antiretroviral therapy (ART) [4].
1999	– WHO announced that HIV/AIDS was the fourth leading cause of death worldwide, and the first in Africa. Approximately 33 million people were HIV-positive globally, and 14 million died due to AIDS [30].
2000	– The United Nations adopted the Millenium Development Goals (MDGs), including a specific goal to combat HIV/AIDS, malaria and tuberculosis (MDG 6) [31].

Table 2.1. Key historical events of HIV/AIDS between 1981 and 2019 (*continued from previous page*).

Year	Key historical event
2001	– The United Nations General Assembly meeting called for the creation of the Global Fund. – Discounted and generic forms of ARVs were produced for developing countries [4].
2002	– The Global Fund was established. – HIV/AIDS was the fourth leading cause of global death, and the first in sub-Saharan Africa [4]. – WHO issued guidelines for: 1) scaling up ART in resource-limited settings [32] and 2) monitoring and evaluating national AIDS programmes [33].
2003	– WHO announced the "3 by 5" initiative: 3 million people being treated by 2005 [34].
2004	– UNAIDS launched the Global Coalition on Women and AIDS [4]. – WHO published guidelines on the use of ART for treating pregnant women and preventing HIV infection in infants [35].
2006	– Male circumcision was shown to reduce the risk of HIV transmission via heterosexual intercourse by 60% [36]. WHO and UNAIDS highlighted the importance of male circumcision in areas with high HIV and low male circumcision prevalence [37]. – WHO updated guidelines on the use of ART in pregnant women [38] and infants and children with HIV [39].
2007	– WHO in collaboration with UNAIDS released guidelines on: 1) post-exposure prophylaxis to prevent HIV infection [40], and 2) provider-initiated HIV testing and counselling in health facilities [41].
2009	– UNAIDS reported a 17% decline in new HIV infections in the past decade [4]. – WHO issued guidelines on nutritional care for HIV-positive children [42].
2010	– Tenofovir vaginal gel was shown to be safe and effective in reducing the risk of HIV infection in women by 39% [43]. – WHO, UNAIDS and the United Nations Children's Fund (UNICEF) published an annual Universal Access report for low and middle-income countries (LMICs): approximately 5.25 million people were receiving ART and 1.2 million people started treatment in 2009 [44]. – WHO updated guidelines on the use of ART in pregnant women [45], adults and adolescents [46], and infants and children [47].
2011	– The United Nations launched a global plan to eliminate MTCT of HIV and keep mothers alive. – FDA approved Complera, a fixed-dose combination (FDC) of emtricitabine, rilpivirine and tenofovir disoproxil fumarate [4]. – The results of HIV Prevention Trials Network (HPTN) 052 Trial showed that early initiation of ART reduced the risk of HIV transmission by 96% among serodiscordant couples [48].
2012	– FDA approved Truvada, an FDC of emtricitabine and tenofovir disoproxil fumarate, for pre-exposure prophylaxis (PrEP) [4]. – For the first time, the majority (54%) of HIV-positive people in LMICs were on ART [49]. – WHO published guidelines on: 1) PrEP for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV [50] and 2) prevention and treatment of HIV for sex workers in LMICs [51].

Table 2.1. Key historical events of HIV/AIDS between 1981 and 2019 (*continued from previous page*).

Year	Key historical event
2013	– UNAIDS estimated that, globally, 35.3 million people were HIV-positive and 2.3 million were newly infected. AIDS-related deaths had declined 30% since their peak in 2005. UNAIDS also reported a 50% reduction in new HIV infections in 25 LMICs, and a 63% increase in ART coverage in the past two years [52]. – WHO updated guidelines on the use of ART in pregnant and breastfeeding women, including option B and B+ [53].
2014	– UNAIDS launched the ambitious 90-90-90 targets by 2020: 90% of all HIV-positive people to be diagnosed, 90% of those diagnosed to be receiving sustained ART, 90% of those on ART to be achieving viral suppression [54]. – WHO and UNAIDS published guidelines on: 1) HIV prevention, diagnosis, treatment and care for key populations [55] and 2) HIV mortality measurement [56].
2015	– UNAIDS announced that the targets for MDG 6 had been achieved [57]. – UNAIDS published: 1) 2015 World AIDS Day report – an estimated 15.8 million HIV-positive people were on ART [58], and 2) 2016–2021 strategy – on the fast-track to end AIDS epidemic by 2030 [59]. – WHO issued the "treat all" recommendation: an immediate initiation of lifelong ART in all HIV-positive people, including pregnant and breastfeeding women, irrespective of clinical and immunological conditions [60].
2016	– UNAIDS stated that 18.2 million HIV-positive people were on ART [61]. – A study showed a high proportion of drug resistance among patients on first-line tenofovir-based ART with virological failure [62]. WHO issued a report on early warning indicators of HIV drug resistance [63].
2017	– More than half of all HIV-positive people worldwide, corresponding to 19.5 million, received ART [64]. – The Prevention Access Campaign launched the Undetectable=Untransmissable (U=U) slogan, suggesting that virally suppressed HIV-positive people cannot sexually transmit the virus to their partners [65]. – WHO considered an ART transition from efavirenz-based to dolutegravir-based ART in HIV programmes [66]. – WHO issued guidelines on HIV drug resistance [67].
2018	– UNAIDS estimated that, globally, 37.3 million people were HIV-positive, of whom, 62% received ART. Furthermore, 1.7 million were newly infected and 730,000 died due to AIDS. Approximately 1.3 million pregnant women were HIV-positive, of whom, 84% were on ART [68].
2019	– Compared to last year, number of HIV-positive people worldwide rose to 38 million, of whom, 67% received ART. New HIV infections remained at 1.7 million and AIDS-related deaths dropped to 690,000. Number of HIV-positive pregnant women remained at 1.3 million, of whom, 85% were on ART [68]. – WHO issued recommendations on first- and second-line ART regimens [69].

Appendix 2.2

HIV-1 molecular structure and transmission.

Table 2.2. Regulatory and accessory genes of HIV-1.

Gene	Protein	Function
tat	Transcriptional activator	Promotes the expression of all viral proteins.
rev	Regulator of virus protein expression	Facilitates the export of non-spliced and partially spliced viral mRNA from nucleus to cytoplasm
vif	Viral infectivity protein	Enhances virus infectivity.
vpr	Viral protein R	Involves in virus infectivity, G2 arrest in cell cycle and nuclear import.
vpu	Viral protein U	Enhances virion release from the infected cells and control of CD4 degradation.
nef	Negative regulating factor	Downregulates the CD4 receptor, enhances virus infectivity, involves in cellular signal transduction and activation.
Source: Fanales-Belasio et al. [70], Ferguson et al. [71], Schwartz et al. [72].		

Table 2.3. Per-contact risk estimates of HIV transmission from anal intercourse.

Authors	Study design (sample size)	Population	Type of anal intercourse	Per-contact transmission probability % (95% CI)
Baggaley et al. 2010 [73]	Meta-analysis (16 studies)	MSM and heterosexual	Receptive	1.40 (0.20, 2.50)
Boily et al. 2009 [74]	Meta-analysis (2 studies)	Heterosexual	Receptive	1.70 (0.30, 8.90)
Fox et al. 2011 [75]	Systematic review (9 studies)	MSM and heterosexual	Receptive	0.50 (95% CI not reported)
	Systematic review (6 studies)	MSM	Insertive	0.07 (95% CI not reported)
Jin et al. 2010[§] [76]	Prospective cohort (N=1,427)	MSM	Receptive with ejaculation	1.43 (0.48, 2.85)
			Receptive with withdrawal	0.65 (0.15, 1.53)
			Insertive	0.16 (0.05, 2.9)
Vittinghoff et al. 1999 [77]	Prospective cohort (N=2,189)	MSM and bisexual men	Insertive[ǀ]	0.06 (0.02, 0.19)
[§]Conducted in the era of highly active antiretroviral therapy. [ǀ]Unprotected insertive anal intercourse with an HIV-positive or unknown serostatus partner. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men.				

Table 2.4. Per-contact risk estimates of HIV transmission from vaginal intercourse.

Authors	Study design (sample size)	Type of vaginal intercourse	Per-contact transmission probability % (95% CI)
Boily et al. 2009 [74]	Meta-analysis (35 studies)	Unspecified	0.18 (0.11, 0.30)
	Meta-analysis (5 studies)	Receptive	0.08 (0.05, 0.11)
Fox et al. 2011 [75]	Systematic review (13 studies)	Receptive	0.1 (95% CI not reported)
	Systematic review (12 studies)	Insertive	0.05 (95% CI not reported)
Hughes et al. 2012 [78]	Prospective cohort (N=3,297 couples)	Receptive	0.19 (0.10, 0.37)
		Insertive	0.10 (0.06, 0.17)
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.			

Table 2.5. Per-injection risk estimates of HIV transmission from contaminated needle and syringe.

Authors	Study design	Type of exposure	Per-injection transmission probability % (95% CI)
Baggaley et al. 2006 [79]	Meta-analysis (21 studies)	Accidental percutaneous injury	0.23 (0.00, 0.46)
Hudgens et al. 2001 [80]	Mathematical model	Use of contaminated needle and syringe	0.84 (0.70, 1.00)
Kaplan et al. 1992 [81]	Mathematical model	Use of contaminated needle syringe	0.67 (95% CI not reported)
Lee et al. 2009 [82]	Literature review	Accidental percutaneous injury	0.3% (95% CI not applicable)
Patz et al. 1995 [83]	Literature review	Accidental percutaneous injury	Range: 0.3 to 0.4
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.			

Table 2.6. Risk estimates of HIV transmission from sharing needles and syringes.

Authors	Study design (sample size)	Type of needle/syringe sharing	Risk estimate (95% CI)
Bruneau et al. 2011 [84]	Prospective cohort (N=2,137)	Unspecified	Adjusted HR 3.03 (2.08, 4.41)
Miller et al. 2006 [85]	Prospective cohort (N=1,013)	Receptive sharing	Adjusted HR 1.48 (1.00, 2.21)
Roy et al. 2011 [86]	Prospective cohort (N=2,671)	Receptive sharing	Adjusted HR 2.36 (1.83, 3.03)
Wylie et al. 2006 [87]	Cross sectional (N=360)	Receptive sharing	Adjusted OR 8.7 (2.00, 38.5)
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; OR, odds ratio.			

Table 2.7. Rates of mother-to-child transmission of HIV pre- and post-HAART era.

Authors	Setting	Period	Study design (sample size)	Rate of MTCT (%)	
				Pre-HAART	Post-HAART
Low and middle-income countries					
Bhatta et al. 2020 [88]	India	2000-2011	Meta-analysis (10 studies)		8.8
Desta et al. 2019 [89]	Ethiopia	2006	Cross sectional (N=340)		2.1
Dryden-Peterson et al. 2011 [90]	Botswana	2009-2010	Retrospective cohort (N=415)		2.4
Ekpini et al. 1997 [91]	Côte d'Ivoire	1990-1994	Prospective cohort (N=139)	23.7	
Endalamaw et al. 2018 [92]	Ethiopia	2004-2015	Meta-analysis (18 studies)		11.4
John et al. 1996 [93]	9 sub-Saharan African countries	Before 1996	Literature review	22.0-43.0	
Kesho Bora Study Group. 2010 [94]	Kenya	2005-2006	Prospective cohort (N=236)		1.7
Kumar et al. 1995 [95]	India	1990-1993	Prospective cohort (N=143)	48.0	
Lallemant et al. 1989 [96]	Democratic Republic of Congo	1987-1989	Prospective cohort (N=35)	25.7	
Nikuze et al. 2015 [97]	Sub-Saharan Africa	Unspecified (post-HAART)	Meta-analysis (12 studies)		4.0
Powis et al. 2016 [98]	Botswana	2001-2003, 2006-2008	Prospective cohort (N=819)		6.1
Ryder et al. 1988 [99]	4 sub-Saharan African countries	1985-1988	Literature review	4.0-13.5	
Santosa et al. 2019 [100]	South Africa	2013-2016	Prospective cohort (N=229)		0
Semba et al. 1994 [101]	Malawi	1989-1991	Prospective cohort (N=338)	21.9	
Shapiro et al. 2010 [102]	Botswana	2006-2008	Prospective cohort (N=730)		0.8
van der Merwe et al. 2011 [103]	South Africa	2004-2007	Retrospective cohort (n=828)		5.4
Working Group on MTCT of HIV. 1995 [104]	Latin America & Caribbean, sub-Saharan Africa	Up to 1993	Prospective cohort (N=2,205)	13.0-42.0	
High-income countries					
Birkhead et al. 2010 [105]	USA	1997-2008	Surveillance data (N=8,972)		4.2
European Collaborative Study 2001 [106]	9 European countries	Up to 1994	Prospective cohort (N=1,620)	15.5	
		After 1998	Prospective cohort (N=156)		2.6
Forbes et al. 2012 [107]	Canada	1990-1996	Retrospective cohort (N=362)	20.2	
		1997-2010	Retrospective cohort (N=2,297)		2.9

Table 2.7. Rates of mother-to-child transmission of HIV pre- and post-HAART era (*continued from previous page*).

Authors	Setting	Period	Study design (sample size)	Rate of MTCT (%)	
				Pre-HAART	Post-HAART
Gabiano et al. 1992 [108]	Italy	Up to 1991	Prospective cohort (N=574)	23.9	
John et al. 1996 [93]	USA	Before 1996	Literature review	17.0-30.0	
Mandelbrot et al. 1998 [109]	France	1985-1996	Retrospective cohort (N=2,819)	13.7	
Mandelbrot et al. 2015 [110]	France	2000-2011	Retrospective cohort (N=8,071)		0.6
Mayaux et al. 1995 [111]	France	1986-1993	Prospective cohort (N=848)	20.2	
McDonald et al. 2009 [112]	Australia	1982-1994	Surveillance data (N=151)	24.5	
		1999-2006	Surveillance data (N=196)		5.6
Nave´r et al. 2006 [113]	Sweden	1985-1993	Prospective cohort (N=87)	24.7	
		1999-2003	Prospective cohort (N=178)		0.6
Samuel et al. 2014 [114]	UK	2004-2010	Retrospective cohort (N=97)		1.0
Townsend et al. 2008 [115]	UK, Ireland	2000-2006	Surveillance data (N=5,151)		1.2
Working Group on MTCT of HIV. 1995 [104]	European countries, USA	Up to 1993	Prospective cohort (N=2,516)	14-25	

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; UK, United Kingdom; USA, United States of America.

Appendix 2.3

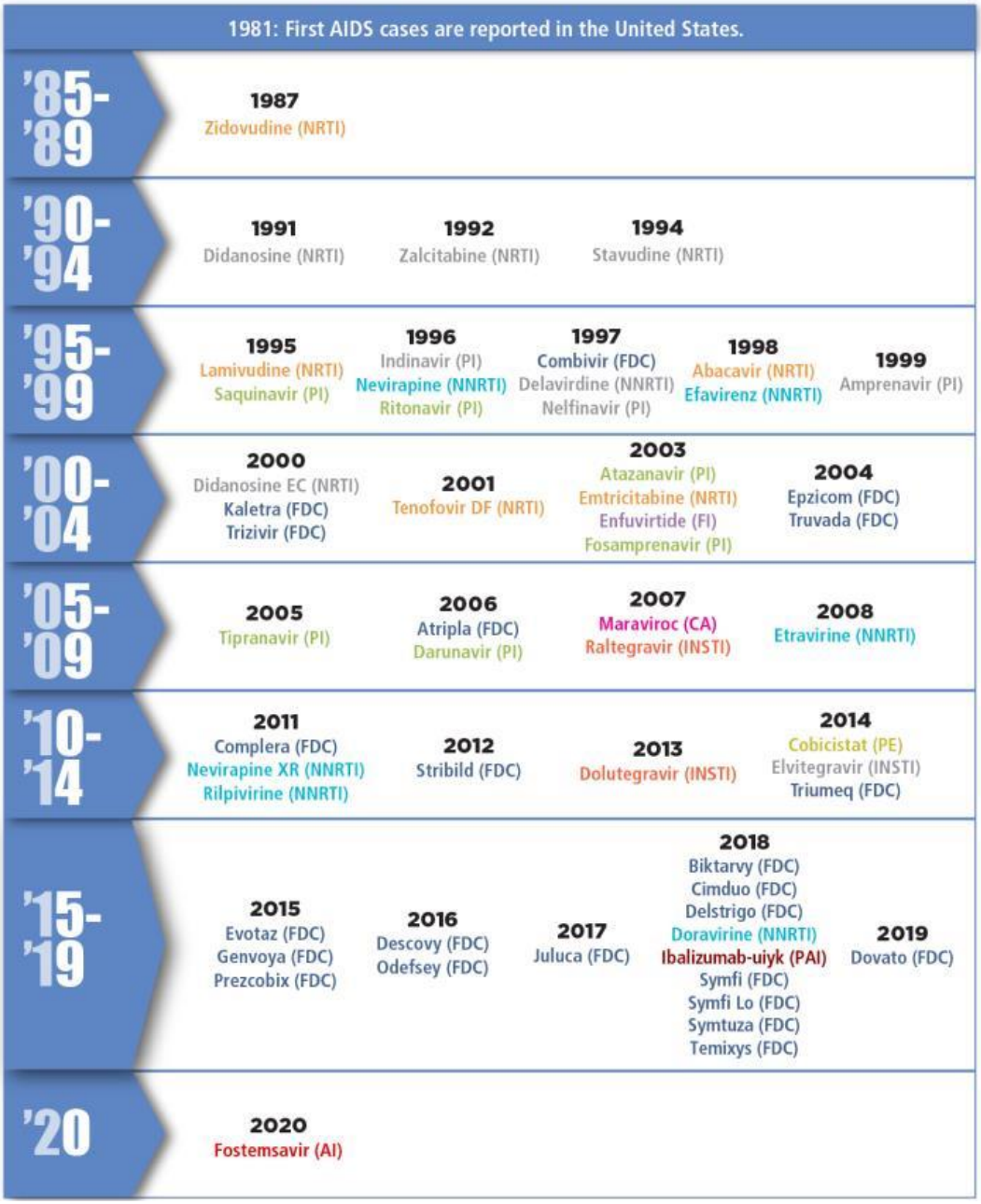
Antiretroviral therapy.

Table 2.8. Fixed-dose combination of HIV medicines approved by the US Food Drug and Administration.

Drug name	Trade name
Abacavir and lamivudine (ABC/3TC)	Epzicom
Abacavir, dolutegravir and lamivudine (ABC/DTG/3TC)	Triumeq
Abacavir, lamivudine and zidovudine (ABC/3TC/ZDV)	Trizivir
Atazanavir and cobicistat (ATV/COBI)	Evotaz
Bictegravir, emtricitabine and tenofovir alafenamide (BIC/FTC/TAF)	Biktarvy
Darunavir and cobicistat (DRV/COBI)	Prezcobix
Darunavir, cobicistat, emtricitabine and tenofovir alafenamide (DRV/COBI/FTC/TAF)	Symtuza
Dolutegravir and lamivudine (DTG/3TC)	Dovato
Dolutegravir and rilpivirine (DTG/RPV)	Juluca
Doravirine, lamivudine and tenofovir disoproxil fumarate (DOR/3TC/TDF)	Delstrigo
Efevirenz, emtricitabine and tenofovir disoproxil fumarate (EFV/FTC/TDF)	Atripla
Efevirenz, lamivudine and tenofovir disoproxil fumarate (EFV/3TC/TDF)	Symfi
Elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide (EVG/COBI/FTC/TAF)	Genvoya
Elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)	Stribild
Emtricitabine, rilpivirine and tenofovir alafenamide (FTC/RPV/TAF)	Odefsey
Emtricitabine, rilpivirine and tenofovir disoproxil furmarate (FTC/RPV/TDF)	Complera
Emtricitabine and tenofovir alafenamide (FTC/TAF)	Descovy
Emtricitabine and tenofovir disoproxil furmarate (FTC/TDF)	Truvada
Lamivudine and tenofovir disoproxil furmarate (3TC/TDF)	Cimduo
Lamivudine and zidovudine (3TC/ZDV)	Combivir
Lopinavir and ritonavir (LPV/r, LPV/RTV)	Kaletra

Abbreviation: HIV, human immunodeficiency virus.

Table 2.9. Timeline of all FDA approval for HIV medicines.



Abbreviations: AI, attachment inhibitor; CA, CCR5 antagonist; FDC, fixed-dose combination; FI, fusion inhibitor; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/ nucleotide reverse transcriptase inhibitor; PAI, post-attachment inhibitor; PE, pharmacokinetic enhancer; PI, protease inhibitor.

Appendix 2.4

Phenotypic classification of preterm birth.

Table 2.10. Phenotypic components of preterm birth syndrome proposed by Esplin et al. [116].

Phenotypes	Strong evidence	Moderate evidence	Possible evidence
Infection/ inflammation	–Histologic chorioamnionitis or funisitis –Positive placental culture or presence of placental viral inclusions	–Clinical chorioamnionitis requiring intrapartum antibiotic –Placental pathology positive for deciduitis, villitis, microabses, arteritis, and/or phlebitis	–Clinical endometritis requiring post-partum antibiotic –Major antenatal maternal systemic infection (pneumonia, pyelonephritis, pancreatitis, hepatitis) –Symptomatic urinary tract infection –Sexually transmitted disease (chlamydia, gonorrhea, trichomoniasis, HIV) diagnosed during pregnancy
Decidual haemorrhage	–Hemosiderin deposits or tightly adherent clot on placental pathology –At least 25% haemorrhage on fetal or maternal interface on placental pathology	–Placental pathology demonstrating 1-25% or unspecified percentage of haemorrhage on fetal or maternal interface –Active vaginal bleeding plus at least one of the following: non-reassuring fetal heart tones, uterine tenderness, or uterine tachysystole –Clinical diagnosis of abruption requiring delivery	–Trauma to abdomen or motor vehicle accident during pregnancy –Vaginal bleeding during pregnancy –Placenta praevia
Maternal stress	–Moderate to severe depression/anxiety requiring medication during pregnancy	–Beck Depression Index score indicates severe depression –Perceived stress score “very high”, or life stressor questionnaire “severe distress”	–Mild to moderate depression/anxiety not requiring medication during pregnancy –Illicit drug use or current binge alcohol use during pregnancy –High risk socioeconomic risk factor: income less than poverty level, less than high school degree
Cervical insufficiency	–Cervical dilatation ≥2cm before 28 weeks’ gestation in the absence of labour –Cervical length <0.5cm before 28 weeks’ gestation in the absence of labour –At least one pregnancy loss before 24 weeks’ gestation due to painless cervical dilatation	–Cervical length <1.5cm before 28 weeks’ gestation in the absence of labour –Cervical length 1.5-2.5cm before 28 weeks’ gestation and hourglassing membranes/marked funneling	–Cervical length 1.5-2.5cm before 28 weeks’ gestation in the absence of labour –History of cervical conization or loop electro-excision procedure

Table 2.10. Phenotypic components of preterm birth syndrome proposed by Esplin et al. [116] (*continued from previous page*).

Phenotypes	Strong evidence	Moderate evidence	Possible evidence
Uterine distention	Not available	–Polyhydramnios (four quadrant amniotic fluid index >25cm or single deepest pocket >8cm) –Birth weight >90% for gestational age	–Sonographically-confirmed uterine fibroids –Placental weight >90% for gestational age
Placental dysfunction	–Birth weight <3% for gestational age and gender –Placental weight <3% for gestational age –At least 25% placental infarction on pathology –Reverse end diastolic flow on cord Doppler prior to delivery –Preeclampsia with severe features or eclampsia	–Birth weight <10% for gestational age and gender –Placental weight <10% for gestational age –Absent end diastolic flow on cord Doppler prior to delivery –Any placental infarction with no percentage listed or <25% on placental pathology –Four quadrant amniotic fluid index <5cm or single deepest pocket <2cm on ultrasound –Preeclampsia without severe features	–Placental calcifications on pathology –Umbilical artery cord Doppler S/D ratio >4cm/sec but no evidence of absent- or reversed-end diastolic flow –Meconium staining on placental pathology –Velamentous cord insertion on placental pathology
Preterm prelabour rupture of membranes	–Preterm prelabour rupture of membranes diagnosed with sterile speculum examination, dye test, or amnisure at least 48 hours prior to the onset of labour	–Preterm prelabour rupture of membranes diagnosed with sterile speculum examination, dye test, or amnisure 12-48 hours prior to the onset of labour	–History of preterm prelabour rupture of membranes and delivery <37 weeks' gestation in a prior pregnancy
Maternal comorbidities	–Class B or higher diabetes mellitus –Chronic hypertension –Systemic lupus erythematosus –Antiphospholipid antibody syndrome –Chronic renal failure or insufficiency	–Gestational diabetes in the current gestation –Other medical condition affecting a major organ system, not otherwise specified, i.e. pulmonary disease, renal disease, autoimmune disease, history of seizures	Not available
Familial	–At least one first degree relative with a history of spontaneous preterm birth	–At least one first degree relative with a history of medically preterm birth	–At least one second degree relative with a history of medically preterm birth

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Appendix 3.1 : ART and perinatal outcomes systematic review protocol.

Appendix 3.2 : Specific search strategy.

Appendix 3.3 : General search strategy.

Appendix 3.4 : Adapted Newcastle-Ottawa quality assessment checklist for cohort studies included in the systematic review.

Appendix 3.5 : Adapted Newcastle-Ottawa quality assessment checklist for case-control studies included in the systematic review.

Appendix 3.6 : Characteristics of studies included in the systematic review.

Appendix 3.7 : Sensitivity analyses and summary of meta-analysis results: effect of maternal HIV/ART on adverse perinatal outcomes.

Appendix 3.8 : Sensitivity analyses and summary of meta-analysis results: effect of maternal ART on adverse perinatal outcomes.

Appendix 3.9 : Sensitivity analyses and summary of meta-analysis results: effect of ART complexity on adverse perinatal outcomes.

Appendix 3.10 : Sensitivity analyses and summary of meta-analysis results: effect of ART class on adverse perinatal outcomes.

Appendix 3.11 : Sensitivity analyses and summary of meta-analysis results: effect of timing of ART initiation on adverse perinatal outcomes.

Appendix 3.1

ART and perinatal outcomes systematic review protocol.

Antiretroviral therapy and adverse perinatal outcomes: a systematic review and meta-analysis.

1. Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 17.8 million women aged 15 years and over were living with human immunodeficiency virus (HIV) in 2016 [1]; among them, approximately 1.5 million were pregnant [2]. HIV-infected pregnant or breastfeeding women can transmit HIV to their fetuses or infants, and without any intervention, mother-to-child transmission (MTCT) rates range from 15% to 45% [3]. In the absence of any treatment, around 35% and more than 50% of HIV-infected African children died by the age of 1 year and 2 years, respectively [4]. In addition, in their systematic review and meta-analysis, Wedi COO et al. [5] reported that untreated maternal HIV infection was significantly associated with a higher risk of preterm birth (PTB), low birth weight (LBW), small for gestational age (SGA) and stillbirth.

Since 2002, the World Health Organization (WHO) has developed guidelines on the use of antiretroviral therapy (ART) for adults living with HIV, including pregnant women. In 2010, WHO recommended lifelong ART for all HIV-infected pregnant women with CD4 count ≤350 cells/μL (irrespective of clinical status)

and two options of short-term antiretroviral (ARV) prophylaxis for women with CD4 count >350 cells/μL (option A and option B). Option A recommended *antepartum* zidovudine monotherapy starting from 14 weeks' gestation, *intrapartum* single-dose nevirapine plus the first dose of zidovudine/lamivudine, and *postpartum* daily zidovudine/lamivudine for 7 days. Option B recommended triple ARVs starting from 14 weeks' gestation and continued until the period of MTCT risk has ended [6]. In 2012, a third option (option B+) was recommended: lifelong triple ARVs for all HIV-infected pregnant women, regardless of CD4 count [7]. In 2013, WHO published new guidelines with two recommendations. The first recommendation was lifelong ART (i.e. triple ARVs) for all HIV-infected pregnant and breastfeeding women, irrespective of CD4 count and clinical status (referring to "option B+" in the previous guidelines). The second recommendation was lifelong ART only for HIV-infected pregnant and breastfeeding women eligible for such treatment (CD4 count ≤500 cells/μL, or HIV clinical stage 3 or 4); and for those not eligible for the treatment, ART should be stopped after the period of MTCT risk (referring to "option B" in the previous guidelines) [8]. Following the results of the TEMPRANO trial [9] which showed that initiating ART at CD4 counts >500 cells/μL was associated with less severe HIV-related morbidity/mortality (a composite outcome of death, AIDS diseases and non-AIDS diseases, such as cancer and bacterial diseases), in 2015, WHO published new guidelines with a "treat all" recommendation: immediate initiation of lifelong ART for all HIV-infected people, including pregnant and breastfeeding women [10]. The administration of ART in pregnancy has reduced new HIV infections among children aged 0-14 years by approximately 63% between 2005

and 2016, from 430,000 to 160,000 [11]. Furthermore, ART use has decreased AIDS-related mortalities among women of reproductive age (15-49 years) by 43%, from 440,000 deaths in 2009 to 250,000 deaths in 2015 [12]. Given these two benefits, WHO has expanded ART coverage; in 2016, about 76% of pregnant women worldwide received ART [11]. Altogether, the "treat all" recommendation, the expansion of ART coverage have brought us to face three realities: 1) more women are on ART when they become pregnant, 2) more fetuses are being exposed to ART *in utero* and 3) the duration of that exposure is longer.

Although the benefits of ART in reducing MTCT rates and AIDS-related maternal mortalities are indisputable, the effects of ART exposure *in utero* on adverse perinatal outcomes remain controversial. Existing studies to date have shown conflicting results related to regimen complexity (number of drugs), type of regimen (class of drugs) and timing of ART initiation. Regarding regimen complexity, Chen YJ et al. [13] showed that antenatally initiated highly-active-antiretroviral-therapy (HAART) significantly increased the risk of PTB (adjusted OR: 1.40; 95%CI: 1.20, 1.90), SGA (adjusted OR: 1.50; 95%CI: 1.20, 1.90) and stillbirth (adjusted OR: 2.50; 95%CI: 1.60, 3.90) compared to antenatally initiated zidovudine monotherapy. However, Li N and colleagues [14] found that antenatally initiated HAART was significantly associated with a higher risk of severe SGA (adjusted RR: 1.47; 95%CI: 1.09, 1.98), but not with PTB and SGA, compared to antenatally initiated zidovudine monotherapy. With regard to class of drugs, Cotter AM et al. [15] showed that protease inhibitor (PI)-based

combination therapy was significantly associated with a higher risk of PTB compared with non-PI-based combination therapy (adjusted OR: 1.80; 95%CI: 1.10, 3.00). On the other hand, Toumala RE et al. [16] observed that PI-based combination therapy was not significantly associated with an increased risk of PTB compared with non-PI-based combination therapy (adjusted OR: 1.80; 95%CI: 0.94, 3.43). Regarding timing of ART initiation, Machado ES and colleagues [17] reported that women who initiated HAART before pregnancy had a greater risk of PTB (adjusted OR: 5.06; 95%CI: 1.50, 17.06) and LBW (adjusted OR: 3.60; 95%CI: 1.71, 7.70) than those initiated HAART during antenatal period. Another study, however, found that an increased risk of PTB was observed among women initiated HAART after conception compared to those initiated HAART before conception (adjusted OR: 2.52; 95%CI: 1.22, 5.20) [18].

Several studies have been conducted to systematically review and synthesise the aforementioned conflicting evidence. In 2007, Kourtis AP et al. [19] investigated whether the use of ART in HIV-infected pregnant women was associated with an increased risk of PTB. They included 13 prospective and 1 retrospective cohort studies (including Cotter AM et al. [15] and Toumala RE et al. [16]) published until May 2006. They showed that a higher risk of PTB was not found in HIV-infected pregnant women who received monotherapy or any combination therapy or PI-based combination therapy or any ART regimen compared to untreated HIV-infected pregnant women. Combination therapy was also not significantly associated with a higher risk of PTB compared to monotherapy. However, they found that PI-based (*versus* non-PI-based) combination therapy and

preconception/first-trimester initiation of ART (*versus* second- or third-trimester initiation) significantly increased PTB risk. We need to be cautious in interpreting these results because of inherent limitations of this systematic review. Firstly, all the included studies are observational in nature and prone to bias; only 6 of 14 studies adjusted for potential confounders (CD4 count, maternal age, drug use, smoking, alcohol consumption, etc.). Secondly, regarding timing of ART initiation, they combined preconception and first-trimester initiation as one composite variable "early initiation", and compared this variable with second- or third-trimester initiation. Thus, it is ambiguous whether they compared preconception *versus* antenatal initiation, or first-trimester *versus* after first-trimester initiation. In addition, their study was conducted a decade ago; during that period, guidelines have been updated, for example, WHO revised ART guidelines three times (in 2010, 2013 and 2015) over the last decade. Following the implementation of these guidelines, several studies were conducted and they were not included in Kourtis AP and colleagues' review.

A very recent systematic review investigating the safety of tenofovir disoproxil fumarate (TDF)-based ART (*versus* non-TDF) in HIV-infected pregnant women was carried out by Nachega JB et al [20]. They found that the risk of PTB (pooled RR: 0.90; 95%CI: 0.81, 099) and stillbirth (pooled RR: 0.60; 95%CI: 0.43, 0.84) were significantly lower in women received TDF-based ART than those received non-TDF-based ART. In addition, they found that TDF-based ART was significantly associated with an increased risk of neonatal mortality (<14 days) compared to non-TDF-based ART (pooled RR: 5.64; 95%CI: 1.70, 18.79). Using

the treatment comparison groups of “TDF” *versus* “non-TDF”, however, may result in not taking into account the effects of regimen complexity, type of regimen and timing of ART initiation on the risk of adverse perinatal outcomes. Both groups contained any types of ART: monotherapy or dual therapy or HAART, PI-based or non-PI-based ART, preconception or antenatal initiation of ART. Among four studies included in the analysis of PTB, one study specified that 100% of women received triple therapy in TDF group, however, 50% of women had triple therapy and 50% zidovudine monotherapy plus single-dose nevirapine in the non-TDF group. One study mentioned that the proportion of women that received PI-based ART was higher in the TDF group than non-TDF group (91% *versus* 79%), while other studies did not mention this. One study specified that the proportion of women that initiated ART before conception was higher in the non-TDF group (89.2% of 2249) than TDF group (13.5% of 1219).

The association between ART initiation (preconception *versus* antenatal) and adverse perinatal outcomes was assessed by Uthman OA and colleagues [21]. In their systematic review and meta-analysis, 11 cohort studies (including Chen YJ et al. [13], Li N et al. [14], Machado ES et al. [17] and Short CES et al. [18]) were included. They reported that preconception initiation of ART was significantly associated with an increased risk of PTB, very PTB and LBW compared to antenatal initiation. However, this review was unable to show which ART regimen(s) significantly increased the risk of PTB, very PTB and LBW if initiated before conception, whether only PI-based or non-PI-based or both classes, or whether only HAART or dual therapy or both complexities. In addition, there

were two important sources of bias that could affect the findings of this review. First, women with preconception initiation of ART may have: 1) more advanced HIV, hence, they initiated ART before conception; 2) more risk factors for adverse perinatal outcomes (e.g. more likely to be older and to have a history of adverse perinatal outcome) than those with antenatal initiation. Second, most of the included studies did not provide data on gestational age of ART initiation, therefore, women with the outcome of PTB may be excluded from the group of women with antenatal initiation if they had not yet commenced ART during pregnancy [22].

In 2013, the US Food & Drug Administration (FDA) approved Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), to be used in combination therapy with other antiretroviral drugs for the treatment of HIV-1 infection in adults and adolescents [23]. The 2015 WHO guidelines recommended DTG-based ART as an alternative first-line regimen in adults and adolescents, but not in pregnant or breastfeeding women [10]. In July 2017, WHO published a "technical update" on considerations for antiretrovirals transition, from efavirenz (EFV)-based first-line regimens to DTG-based first-line regimens [24]. In November 2017, WHO announced that DTG would soon be available in a fixed-dose combination with lamivudine (3TC) and TDF (DTG/3TC/TDF) at a lower price, and many countries will adopt DTG-based ART as a first-line regimen [25]. Preliminary results on DTG use in HIV-infected pregnant women are reassuring. Zash R et al. [26] conducted a retrospective study involving 5438 women, and around 16% of them were on DTG-based ART. They found that DTG-based ART

was not significantly associated with a higher risk of PTB, very PTB, SGA, very SGA, stillbirth and neonatal death compared with EFV-based ART. In addition, Vannappagari V et al. [27] showed that the proportions of PTB, LBW and very LBW were comparable between women initiated DTG in first trimester (11.6%, 13%, 4.3% respectively for PTB, LBW, very LBW) compared to second/third trimester (10%, 10%, 4% respectively for PTB, LBW, very LBW). Trahan MJ et al. [28] conducted a retrospective study investigating the outcomes of 14 infants born to mothers treated with raltegravir (RAL; another drug that belongs to INSTI): the means of gestational age and birth weight were 38.5 weeks (± 1.76) and 3200 g (± 540), respectively. Furthermore, Mounce ML et al. [29] carried out a retrospective matched cohort study investigating maternal and infant outcomes associated with INSTI-based compared to PI-based ART in HIV-infected pregnant women. They found that, between infants exposed to INSTI and PI, there were no significant differences in the medians of gestational age at birth (median: 38.0; IQR: 38.0, 39.0 *versus* median: 38.5; IQR: 37.0, 39.0 for INSTI and PI group respectively, p=0.71) and the proportions of LBW (33.3% *versus* 40.0% for INSTI and PI group respectively, p=1.00). However, this analysis was conducted in a small sample size: 7 and 14 women for INSTI and PI groups, respectively. There is no systematic review to date which has assessed the association between INSTI-based ART and adverse perinatal outcomes.

2. Objectives

1. To assess the risks of adverse perinatal outcomes and MTCT in HIV-infected pregnant women receiving antiretroviral therapy (ART).
2. To assess the risks of adverse perinatal outcomes and MTCT in HIV-infected pregnant women receiving different complexities of ART regimens (monotherapy, dual therapy, HAART).
3. To assess the risks of adverse perinatal outcomes and MTCT of HIV infection in HIV-infected pregnant women receiving different classes of ART drugs (NRTI-based, NNRTI-based, INSTI-based, PI-based).
4. To assess the risks of adverse perinatal outcomes and MTCT in HIV-infected pregnant women receiving ART with different timings of initiation (preconception, first-trimester, second-trimester, third-trimester).

3. Methods

3.1 Eligibility criteria

The inclusion and exclusion criteria for studies to be included in the review are summarised in Table 1.

3.1.1 Inclusion criteria

- Participants

  The review will include HIV-infected pregnant women receiving ART during pregnancy. Women of any clinical or immunological stage of HIV disease, any stage of pregnancy, with any sociodemographic characteristics will be eligible for inclusion. Studies which have included participants of interest as a subset of the entire study will be initially included. These studies will then be discussed amongst the reviewers to decide whether these studies are eligible to be included in the review. All countries and settings are eligible for inclusion.

- Exposures

  The review will include studies examining the use of any ART regimen in HIV-infected pregnant women for a duration of at least 30 days. The ART regimens can contain any antiretroviral drugs presented in Table 2 [30]. Studies in which additional medications were administered to all participants in both exposed and comparator groups, such as antenatal multivitamin, are eligible to be included in the review.

Table 1. Inclusion and exclusion criteria.

Components	Inclusion criteria	Exclusion criteria
Participants	HIV-infected pregnant women receiving antenatal ART	Ambiguous eligibility criteria
		HIV-infected pregnant women with co-existing diseases (malaria, tuberculosis), which are imbalanced between exposure and comparator groups
Exposures	Any ART regimen initiated either before or after conception for a duration of at least 30 days	ART exposure is defined as a single-dose ART at delivery
		Duration of antenatal ART exposure is <30 days
		Additional medications during pregnancy (anti-malarial/anti-tuberculosis drugs), which are imbalanced between exposure and comparator groups
Comparators	HIV-uninfected pregnant women	Inappropriate comparator or no comparator
	HIV-infected pregnant women without ART, or with ART for <30 days	
	HIV-infected pregnant women receiving ART different from the exposure group in terms of complexities, classes of drugs and timings of initiation	
Outcomes	Adverse perinatal outcomes: PTB, very PTB, spontaneous PTB, spontaneous very PTB, LBW, very LBW, term LBW, preterm LBW, SGA, very SGA, miscarriage, stillbirth, neonatal death	Outcomes not defined or defined differently from our protocol
	MTCT of HIV infection	
Study designs	Observational studies: – Prospective and retrospective cohort – Case-control – Cross-sectional	Letters or comments to the editor, opinion pieces, case-reports

- Comparators

  Studies will be included in the review if they use any of the following comparators:

  – Untreated HIV-infected pregnant women or HIV-uninfected pregnant women.

  – Any complexities of ART regimens (monotherapy, dual therapy, HAART).

  – Any classes of ART regimens (NRTI-based, NNRTI-based, INSTI-based, PI-based).

  – Any timings of ART initiation [preconception, first-trimester (<14 weeks), second-trimester (14-28 weeks), third-trimester(>28 weeks)].

- Outcomes

  The primary outcomes of interest will include:

  – Preterm birth (PTB): birth $<37^{+0}$ weeks' gestation.

  – Very PTB: birth $<32^{+0}$ weeks' gestation.

  – Spontaneous PTB: spontaneous birth $<37^{+0}$ weeks' gestation.

  – Spontaneous very PTB: spontaneous birth $<32^{+0}$ weeks' gestation.

  – Low birth weight (LBW): birth weight <2500 g.

  – Very LBW: birth weight <1500 g.

  – Term LBW: LBW infants with gestational age $\geq 37^{+0}$ weeks.

  – Preterm LBW: LBW infants with gestational age $<37^{+0}$ weeks.

  – Small for gestational age (SGA): birth weight for gestational age $<10^{th}$ centile of the reference chart used at the study site.

  – Very SGA: birth weight for gestational age $<3^{rd}$ centile.

- Miscarriage: spontaneous expulsion of fetus $<24^{+0}$ completed weeks' gestation.
- Stillbirth: any third trimester delivery of an infant without any signs of life with birth weight ≥1000 g or gestational age $\geq 24^{+0}$ weeks or body length ≥35 cm.
- Neonatal death: the death of an infant in the first 28 days of life.

The secondary outcome of interest will include MTCT, defined as the results of the first HIV test of an infant which indicate *in utero* or *intrapartum* transmission of HIV. We will include studies reporting MTCT if one of the adverse perinatal outcomes was also reported by those studies.

- Study designs

The review will include observational studies (prospective and retrospective cohorts, case-control studies and cross-sectional studies) assessing adverse perinatal outcomes associated with ART use in HIV-infected pregnant women.

Table 2. Antiretroviral drugs approved by FDA for the treatment of HIV-1 infection.

Drug class	Drug name	Trade name
Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)	Abacavir (ABC)	Ziagen®
	Didanosine (ddI)	Videx®
	Emtricitabine (FTC)	Emtriva®
	Lamivudine (3TC)	Epivir®
	Stavudine (d4T)	Zerit®
	Tenofovir disoproxil fumarate (TDF)	Viread®
	Zidovudine (AZT)	Retrovir®
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	Delavirdine (DLV)	Rescriptor®
	Efavirenz (EFV)	Sustiva®
	Etravirine (ETR)	Intelence®
	Nevirapine (NVP)	Viramune®
	Rilpivirine (RPV)	Edurant®
Protease inhibitor (PI)	Atazanavir (ATV)	Reyataz®
	Amprenavir (APV)	Agenerase®
	Darunavir (DRV)	Prezista®
	Fosamprenavir (FPV)	Lexiva®
	Indinavir (IDV)	Crixivan®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Nelfinavir (NFV)	Viracept®
	Saquinavir (SQV)	Invirase®
	Tipranavir (TPV)	Aptivus®
Integrase strand transfer inhibitor (INSTI)	Dolutegravir (DTG)	Tivicay®
	Elvitegravir (EVG)	Vitekta®
	Raltegravir (RAL)	Isentress®
Fusion/entry inhibitor	Enfuvirtide (T-20)	Fuzeon®
CCR5 receptor antagonist	Maraviroc (MVC)	Seizentry®

3.1.2 Exclusion criteria

- Participants

  The following studies will be excluded from the review:

  – Studies which have used ambiguous inclusion and exclusion criteria in recruiting participants.

  – Studies which have recruited participants with co-existing diseases, such as malaria, tuberculosis and syphilis, which are imbalanced between exposure and comparator groups.

  – Studies which have recruited participants with co-existing diseases and are balanced between the two groups will initially be included. A final decision, whether or not these studies are eligible to be included, will be discussed amongst the reviewers.

- Exposures

  Studies will be excluded if:

  – Antenatal ART exposure is defined as a single-dose ART at delivery.

  – The duration of antenatal ART exposure is <30 days.

  – Additional medications (e.g. anti-malarial and anti-tuberculosis drugs) have been administered and are imbalanced between exposure and comparator groups. However, studies will be eligible to be included in the review if all participants in the two groups are receiving the same additional medications and ART regimens are the only differences between these two groups.

- Comparators

  Studies will be excluded from the review if they use an inappropriate comparator or no comparator.

- Outcomes

  Outcomes not defined or defined differently from our protocol.

- Study designs

  Letters or comments to the editor, opinion pieces and case-reports will be excluded.

3.2 Search methods for identification of studies

3.2.1 Electronic databases

A comprehensive and exhaustive search strategy will be developed by a specialist librarian and will be adapted for each electronic database. In order to identify all relevant studies published between January 1980 and January 2018, we will systematically search:

- Major electronic literature databases, including PUBMED, CINAHL, Global Health, EMBASE and the Cochrane Central database.
- Major trial databases, including WHO Clinical Trials database, Pan African Trials database, ClinicalTrials.gov database and ISRCTN register.

We will use both free-text (search in the title, abstract, or text word fields) and controlled vocabulary (e.g. MeSH or Emtree) search terms for HIV, ART, specific adverse perinatal outcomes (“preterm birth or low birth weight or intrauterine

growth restriction or stillbirth" AND "HIV or ART") or terms indicating general pregnancy outcomes ("pregnancy outcome" AND "HIV or ART"). No methodology or language filters will be applied; studies from all countries are eligible for inclusion; full-text articles and abstracts will be considered.

3.2.2 Other resources

Other sources of potentially relevant studies will be the grey literature, including:

- Dissertation databases, such as ProQuest Dissertation and Theses Database.
- Conference abstracts from selected international symposia on HIV/AIDS.
- Electronic or manual searches of bibliographies of retrieved articles or relevant published systematic reviews.

All retrieved articles will be imported into Endnote reference manager, and duplicated articles will be excluded. We will keep a record of all articles excluded in the deduplication process.

3.3 Data collection and quality assessment

3.3.1 Selection of studies

3.3.1.1 Stage 1: Screening of titles and abstracts

Two reviewers will independently screen the titles and abstracts of all retrieved articles from both the electronic and manual searches, in an attempt to identify all potentially relevant articles. At this stage, we will only include articles of prospective and retrospective cohorts, case-control and cross-sectional studies investigating adverse perinatal outcomes associated with ART use in HIV-

infected pregnant women. Irrelevant articles, e.g. letters or comments to the editor, opinion pieces and case-reports, will be excluded. All excluded articles will be recorded along with information why these articles are excluded. Any disagreements at this stage will be resolved through discussion with a third reviewer until a consensus is achieved. We will keep a record regarding how many disagreements are resolved.

3.3.1.2 Stage 2: Screening of full text for eligibility criteria

Full-text version of all potentially relevant articles identified at stage 1 ("Screening of titles and abstracts") will be retrieved. Two reviewers will independently assess each full-text article to decide whether it meets the eligibility criteria based on PECOS (participant, exposure, comparator, outcome, study design) concept (see Table 1). If it is not possible to make a decision because further information is needed, we will correspond with authors to provide further clarification. All articles which do not meet the eligibility criteria will be excluded. All excluded articles will be recorded along with information why these articles are excluded. Any disagreements at this stage will be resolved through discussion with a third reviewer until a consensus is achieved. We will keep a record regarding how many disagreements are resolved.

3.3.2 Data extraction and management

Two reviewers will independently extract study details using a preformulated data extraction tool in Excel™. The following characteristics will be extracted from each included study:

- Publication details, including authors, name of journal, title of article and year of publication.
- Study details, including specific name of study, country of study, country income status, study design, aims and objectives of study, recruitment period, number of study sites, study setting, sample size and methods to estimate gestational age.
- Participant characteristics, including maternal age, race, education, marital status, socioeconomic status, occupational status, income, smoking status, alcohol consumption during pregnancy, illicit drug use, inclusion of teenage pregnancy, body mass index, gravidity/parity, gestational age at recruitment, blood pressure, population characteristics, number of antenatal visits, HIV subtype, stage of HIV disease, CD4 count/percentage at recruitment, viral load at recruitment, CD4 count/percentage at delivery, viral load at delivery, haemoglobin level, mode of delivery or Caesarean section rate and breastfeeding.
- Exposure details, including exposure/ART regimen of interest, treatment/ART comparisons, timing of ART initiation, name of antiretroviral drugs, class of antiretroviral drugs (type of ART regimens), complexity of ART, antenatal duration of ART, indication for treatment initiation, reasons for not receiving ART, treatment adherence, resistance-associated mutations, trimethoprim-sulfamethoxazole prophylaxis, and any other treatment-related information.
- Outcome details, including the numerical data (i.e. raw numbers) of PTB, very PTB, spontaneous PTB, spontaneous very PTB, LBW, very LBW, term LBW, preterm LBW, SGA, very SGA, miscarriage, stillbirth, neonatal death,

congenital anomalies, MTCT, whether or not twin pregnancies included in the analysis and unadjusted and adjusted effect sizes (odds ratio, risk ratio).

Authors will be contacted for further information or data clarifications, as necessary. The extracted data will be compared between the two reviewers. Any disagreements will be resolved through discussion with a third reviewer until a consensus is achieved. We will keep a record regarding how many disagreements are resolved.

3.3.3 Quality assessment of included studies

The assessment of risk of bias will be carried out by two reviewers independently. The summary of this assessment will be presented for each included study and correlated with the observed effect size of each study. The methodological quality will be appraised using an adapted version of the Newcastle-Ottawa Scale [31] which assesses three domains: selection, comparability and outcome/exposure. For cohort and case-control studies, we will employ an adapted version of the Newcastle-Ottawa Scale used by Wedi COO et al. [5], whereas for cross-sectional studies, we will employ such adapted version used by Herzog R, et al [32]. Studies will be classified into three levels of quality as presented in Table 3. Any disagreements will be resolved through discussion with a third reviewer until a consensus is achieved. We will keep a record regarding how many disagreements are resolved.

Table 3. Classification of studies' quality according to the adapted Newcastle-Ottawa Scale.

Quality	Study design		
	Cohorts	**Case-control**	**Cross-sectional**
Good	9 points, all requirements met	10 points, all requirements met	9 points, all requirements met
Average	3 points in “selection” and 3 points in “outcome” domains	4 points in “selection” and 3 points in “exposure” domains	3 points in “selection” and 3 points in “outcome” domains
	≥2 points in “selection” and “outcome” domains, as well as ≥1 point in “comparability” domain	≥3 points in “selection” and ≥2 points in “exposure” domains, as well as ≥1 point in “comparability” domain	≥2 points in “selection” and “outcome” domains, as well as ≥1 point in “comparability” domain
Poor	<2 points in “selection” and/or “outcome” domains	<3 points in “selection” and/or <2 points in “exposure” domains	<2 points in “selection” and/or “outcome” domains
	2 points in “selection” and “outcome” domains, but no points in “comparability” domain	3 points in “selection” and 2 points in “exposure” domains, but no points in “comparability” domain	2 points in “selection” and “outcome” domains, but no points in “comparability” domain

3.4 Analysis

3.4.1 Measures of treatment effect

As we expect that most studies will be either prospective or retrospective cohort studies, pooled risk ratios (RRs) will be calculated as effect measures along with their 95% confidence intervals (CIs) to assess the association between selected binary outcomes and the use of ART in HIV-infected pregnant women.

3.4.2 Unit of analysis

Outcomes will be reported for all possible ART comparisons regarding:

- ART use, e.g. ART-treated *versus* untreated HIV-infected pregnant women.
- ART complexity, e.g. HAART *versus* dual therapy.
- Class of ART, e.g. PI-based *versus* NRTI-based ART.
- Timing of ART initiation, e.g. preconception *versus* antenatal initiation.
- Any combination of ART complexity/class/timing of initiation.

3.4.3 Assessment of heterogeneity

Clinical, methodological and statistical heterogeneity will be examined before conducting meta-analysis. The statistical heterogeneity will be quantified using I^2 statistics. The values of I^2 will be interpreted as follows: no heterogeneity (0%), low heterogeneity (25%-50%), moderate heterogeneity (50%-75%) and high heterogeneity (≥75%) [33]. If major clinical, methodological, or statistical (I^2≥75%) heterogeneity is identified, we plan to do meta-regression evaluating the influence of important factors on the results of meta-analyses. These important factors may include baseline effect sizes (source of statistical heterogeneity),

study setting (source of clinical heterogeneity) and study quality (source of methodological heterogeneity).

3.4.4 Assessment of reporting biases

The potential publication bias will be assessed using a visual inspection of funnel plots and Peters' test or Egger's test, as appropriate [33].

3.4.5 Data synthesis

Pairwise meta-analyses will be conducted when there are two or more studies reporting the same ART comparison and adverse perinatal outcome or MTCT. We will use a random- or fixed-effect model, as appropriate, to calculate the weighted summary RRs along with their 95%CIs. For each outcome of interest, we will use a forest plot to graphically present both the individual study and weighted summary RRs and 95%CIs.

3.4.6 Subgroup analysis

We plan to perform several sub-group analyses to assess the influence of potential covariates on the association between ART use and adverse perinatal outcomes or MTCT in HIV-infected pregnant women:

- Country income status (low, middle and high-income), which will be classified using the World-Bank-country-specific income status [34].
- Methods used to estimate gestational age (the first day of the last menstrual period [LMP] or scan).

- Outcome definition (whether the outcome is defined among “live births” or “all births”).
- Study design (prospective or retrospective cohort).

3.4.7 Sensitivity analysis

We plan to conduct sensitivity analyses in order to assess whether the review findings are dependent on the decisions made during the review process, such as:

- Analyses restricted to women on HAART, or non HAART.
- Analyses restricted to women on PI, or non PI-based ART.

3.4.8 GRADE

The summary of all included studies will be presented in a table which will contain several elements, such as a list of all important outcomes, absolute and relative magnitude of effect, number of participants and studies addressing the outcomes, a grade of the overall quality of the body of evidence for each outcome; as recommended by Cochrane Handbook for Systematic Review of Interventions [35]. The quality of the body of evidence (high, moderate, low and very low) will be graded according to the Grading of Recommendations Assessment, Development and Evaluation System (GRADE) [36].

3.4.9 Reporting of network meta-analysis

We will use the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) extension statement for reporting of systematic reviews

incorporating network meta-analyses, as a guidance to report the findings of our review [37].

Appendix 3.2

Specific search strategy.

Embase search strategy for "preterm birth or low birth weight or intrauterine growth restriction or stillbirth" and "HIV or ART".

Original search carried out on 20 February 2013; rerun on 12 December 2014, 27 July 2015, 26 October 2016, 19 November 2016 and 28 April 2018 to include studies published between 1 January 1980 and 28 April 2018. 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* 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. (monotherap* 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 3.3

General search strategy.

Embase search strategy for "pregnancy outcome" and "HIV or ART".

Original search carried out on 20 March 2013; rerun on 12 December 2014, 27 July 2015, 26 October 2016, 19 November 2016 and 28 April 2018 to include studies published between 1 January 1980 and 28 April 2018. 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 morbidit* or sequelae)).ti,ab.
37. (prenatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
38. (pre-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
39. Perinatal morbidity/
40. (perinatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
41. (peri-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
42. (neonatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.

43. (neo-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
44. (postnatal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
45. (post-natal adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
46. (antepartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
47. (ante-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
48. (intrapartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
49. (intra-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
50. (peripartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
51. (peri-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
52. (postpartum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* or sequelae)).ti,ab.
53. (post-partum adj (outcome* or complication* or consequence* or characteristic* or event* or result* or problem* or morbidit* 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 3.4

Adapted Newcastle-Ottawa quality assessment checklist for cohort studies included in the systematic review (Source: Wedi COO et al. [5]).

A study can be awarded a maximum of 1 point (for items indicated with asterisks) for each numbered criterion within the "selection" and "outcome" domains. A maximum of 2 points can be given for the "comparability" domain.

Selection (maximum 4 points)

1. Representativeness of the exposed cohort (HIV-positive women):
    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 cohort (HIV-negative women, untreated HIV-positive women):
    a. The non-exposed cohort is drawn from the same community as the exposed cohort.*
    b. The non-exposed cohort is drawn from a different source to the exposed cohort.
    c. No description of the derivation of the non-exposed cohort.

3. Ascertainment of exposure (antenatal ART medications):
    a. ART medications as part of the study.*
    b. Information about ART medications confirmed from secure record (e.g. medical records).*
    c. Structured interview, participants reported information about antenatal ART medications.
    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: a history of adverse perinatal outcomes, maternal hypertension, anaemia, illicit drug use, or alcohol consumption.*

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. Gestational age was determined according to early ultrasound (<14 weeks).*

   b. Gestational age was determined by: late ultrasound (≥14 weeks' gestation) or last 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 3.5

Adapted Newcastle-Ottawa quality assessment checklist for case-control studies included in the systematic review (Source: Wedi COO et al. [5]).

A study can be awarded a maximum of 1 point (for items indicated with asterisks) for each numbered criterion within the "selection" and "exposure" domains. A maximum of 2 points can be given for the "comparability" domain.

Selection (maximum 5 points)

1. Is the case definition adequate?
    a. Yes, the cases are defined as women who experience one of the following adverse perinatal outcomes: PTB, very PTB, spontaneous PTB, spontaneous very PTB, LBW, very LBW, term LBW, preterm LBW, SGA, very SGA, miscarriage, stillbirth and neonatal death (as defined by the systematic review protocol).*
    b. Yes, but definition is different to that which is specified in the systematic review 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 adverse perinatal outcomes at delivery: PTB, very PTB, spontaneous PTB, spontaneous very PTB, LBW, very LBW, term LBW, preterm LBW, SGA, very SGA, miscarriage, stillbirth and neonatal death (as defined by the systematic review protocol).*
    b. Different definition to that which is specified in the systematic review 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: a history of adverse perinatal outcomes, maternal hypertension, anaemia, illicit drug use, or alcohol consumption.*

Exposure (maximum 3 points)

1. Is the assessment of exposure valid?
   a. ART medications as part of the study.*
   b. Confirmed from medical records.*
   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 3.6

Characteristics of studies included in the systematic review.

Table 3.1. Characteristics of studies included in the systematic review.

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Adam et al. 2016 [38]	Sudan	1	Retrospective cohort	January 2009 – December 2013	78	69.2% of HIV-positive women were of urban residence. 96.2% presented with a normal CD4 cell count. 57.7% had less than secondary education and 84.6% were housewives.	No	HIV disease stage: not reported. CD4 cell count: 96.2% of women had a CD4 count ≥350 cells/mm^3.	1. HIV negative 2. Any ART with mixed initiation	PTB	Not reported
Chaudhury et al. 2018 [39]	Botswana	4	Prospective cohort	May 2010 – February 2012 and July 2006 – May 2008	592	The study analysed data from the Tshipidi and Mma Bana studies. Mothers were similar with regards to age, education and income across the cohorts and according to ART exposure.	Not reported	Not reported	1. ZDV initiated antenatal 2. HAART (NRTI-based, NNRTI-based and PI-based), mixed initiation	PTB, LBW	Not reported
Chen et al. 2012 [13]	Botswana	6	Retrospective cohort	May 2009 – April 2011	28780	Women recruited from primary and tertiary obstetrical care centres. Cohort representative of the general population. All women delivered at the hospitals. 5.3% of women consumed alcohol and 1.7% smoked during pregnancy.	Yes. Only first born infants of multiple pregnancies included.	Not reported	1. HIV negative 2. Untreated HIV+ 3. ZDV initiated antenatal 4. ZDV+3TC+NVP, mixed initiation 5. ZDV+3TC+LPV/r, mixed initiation	PTB, SGA	LNMP, SFH, ultrasound (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Chetty et al. 2018 [40]	South Africa	7	Retrospective cohort	January 2010 – December 2015	2549	Cohort representative of HIV-infected pregnant women in Hlabisa HIV Treatment and Care Programme, northern KwaZulu-Natal, South Africa. Overall, women had a normal CD4 count >350 cells/mm^3. Most women attended antenatal clinic late in the 3rd trimester.	No	Not reported	1. ZDV initiated antenatal 2. TDF+FTC/3TC+ EFV, mixed initiation 3. ZDV+3TC+NVP, d4T+3TC+NVP, TDF+3TC+NVP; mixed initiation 4. Pre-conception ABC+3TC+EFV, ZDV+3TC+EFV, d4T+3TC+EFV	PTB, LBW, SGA	LNMP, SFH, ultrasound (unspecified), infant birth examination (unspecified)
Dryden-Peterson et al. 2011 [41]	Botswana	2	Retrospective cohort	February 2009 – April 2010	428	The study recruited HIV+ women at a district referral hospital and the largest national hospital. Women were similar with regard to socio-economic status. Women on ZDV were younger than those with HAART.	Yes. Five sets of twins were enrolled.	Not reported	1. ZDV initiated antenatal 2. HAART (NNRTI-based, PI-based), mixed initiation	PTB, LBW, SGA, MTCT	Not reported
Ekouevi et al. 2008 [42]	Ivory Coast	Not reported	Prospective cohort	March 2001 – August 2007	309	Women recruited from antenatal clinics involved in two sequential prevention of MTCT programmes. All women were eligible for HAART.	No	WHO HIV stage: 49.8% of women were on stage 1/2, 50.2% stage 3/4. CD4 cell count: median (IQR): 177 (123, 243) cells/μL; distribution: 64.1% of women had a CD4count <200 cells/μL, 35.9% ≥200 cells/μL.	1. ZDV or ZDV+3TC initiated antenatal 2. ZDV/d4T+3TC+ NVP, mixed initiation	LBW	SFH

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Ezechi et al. 2012 [43]	Nigeria	1	Retrospective cohort	July 2004 – June 2010	1626	The study was conducted at the HIV treatment centre. All HIV+ women enrolled into the PMTCT programme were included. 3.1% and 11.2% of women were <20 and >35 years respectively, 22.8% were nulliparous, 13.5% were not married, 6.9% had BMI <18.5 kg/m^2 and 3.9% diagnosed with reproductive tract infection at delivery.	Yes. 46 of 1649 babies were results of twin gestations.	HIV disease stage: not reported. CD4 cell count: distribution: 19.2% of women had a CD4count <200 cells/μL, 28.2% 200-350 cells/μL, 28.4% 351-500 cells/μL, 24.2% >500 cells/μL.	1. NNRTI-based HAART, mixed initiation 2. PI-based HAART, mixed initiation	sPTB	LNMP
Joseph et al. 2011 [44]	Nigeria	1	Retrospective cohort	January 2008 – June 2009	249	Cohort identified from a hospital database for a tertiary referral centre. All deliveries occurred at a healthcare facility. None of the participants had AIDS.	No	Not reported	1. Untreated HIV+ 2. ZDV+3TC+NVP initiated antenatal	LBW	Not reported
Li et al. 2015 [14]	Tanzania	10	Prospective cohort	November 2004 – September 2011	3232	Participants recruited from hospitals, health centers and dispensaries. Women were treated with HAART if they met WHO stage 4 criteria, or WHO stage 3 criteria with a CD4 count <350 cells/μL, or had a CD4 count <200 cells/μL. All born infants were HIV negative.	Not reported	WHO HIV stage: 22.2% of women on stage 1, 36.6% stage 2, 35.9% stage 3, 5.3% stage 4. CD4 cell count: distribution: 3.6% of women had a CD4count <50 cells/μL, 4.1% 50–<100 cells/μL, 13.1% 100–<200cells/μL, 79.2% ≥200 cells/μL.	1. Untreated HIV+ 2. ZDV initiated antenatal 3. HAART (NNRTI-based, PI-based), mixed initiation	VSGA	LNMP, SFH

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Malaba et al. 2017 [45]	South Africa	1	Prospective cohort	April 2013 – August 2015	1554	The study was conducted among consecutive HIV-positive and HIV-negative women seeking antenatal care at a large, community-based public sector primary care facility. The facility serves a catchment population of around 350000 where antenatal care uptake is high (95%). In 2014, the antenatal HIV seroprevalence was estimated at 30%.	No	Not reported	1. HIV negative 2. HAART (NNRTI-based and PI-based), mixed initiation 3. TDF+FTC+EFV, mixed initiation 4. PI-based HAART, mixed initiation	PTB, VPTB, LBW, VLBW, SGA	LNMP, SFH, ultrasound (unspecified)
Marazzi et al. 2011 [46]	Malawi, Mozambique	Up to 31	Retrospective cohort	July 2005 – June 2009	2941	Cohort identified from a PMTCT programme. Median (IQR) of maternal age was 26.4 (23.1, 30.4) years.	No	HIV disease stage: not reported. CD4 cell count: median (IQR): 357 (234, 518) cells/μL; distribution: 50% of women had a CD4 count <350 cells/μL.	1. Untreated HIV+ 2. HAART (ZDV or d4T-based) initiated antenatal	PTB	LNMP, newborn clinical assessment (unspecified)
Moodley et al. 2016 [47]	South Africa	1	Retrospective cohort	July – December 2011 and January – June 2014	9611	Women were recruited from regional hospital that supports 17 primary health care clinics. The facility has an annual birth rate of 12000. HIV antenatal prevalence was estimated at 40%.	No	HIV disease stage: not reported. CD4 cell count: distribution: 28.5% of women had a CD4 count <200 cells/mm^3, 28.6% 201-350 cells/mm^3, 28.2% 351-500 cells/mm^3, 14.7% >500 cells/mm^3.	1. HIV negative 2. Untreated HIV+ 3. ZDV initiated antenatal 4. TDF+FTC+EFV initiated antenatal 5. d4T+3TC+NVP initiated antenatal	PTB, LBW, SGA	LNMP, ultrasound (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Nlend et al. 2016 [48]	Cameroon	1	Retrospective cohort	2008 – 2011	760	The cohort was conducted at a referral hospital. Women and their babies were routinely monitored in the PMTCT program. By treatment groups, women were similar with regards to age and parity.	No	HIV disease stage: not reported. CD4 cell count: median (IQR): 533 (435, 679) cells/mm^3.	1. ZDV initiated antenatal 2. ZDV+3TC+NVP or PI-based HAART initiated antenatal	PTB, LBW	LNMP, SFH, ultrasound (unspecified)
Olagbuji et al. 2010 [49]	Nigeria	1	Prospective cohort	January 2007 – December 2008	406	Participants were recruited from a tertiary referral centre. All deliveries occurred at a healthcare facility. All women were married. Treated HIV-positive women had a higher parity and were less educated than HIV-negative women.	No	Not reported	1. HIV negative 2. ZDV+3TC+NVP initiated antenatal	LBW	Not reported
Powis et al. 2016 [50]	Botswana	4	Prospective cohort	March 2001 – October 2003 and July 2006 – May 2008	819	The study analysed data from the Mashi and Mma Bana PMTCT studies. Both studies enrolled HIV-1 infected pregnant women regardless of baseline CD4 cell count. By treatment groups, women had the same profile with regards to age, education, gravida, marital and employment status.	No	HIV disease stage: not reported. CD4 cell count: median (IQR): 393 (273, 547) cells/μL.	1. ZDV initiated antenatal 2. HAART (NRTI-based, NNRTI-based, PI-based) initiated antenatal	LBW, MTCT	LNMP and 2^{nd} trimester ultrasound

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Ramokolo et al. 2017 [51]	South Africa	580	Retrospective cohort	October 2012 – May 2013	8778	Consenting mother-infant pairs attending immunization services were consecutively or systematically enrolled, regardless of maternal HIV status. During the study period, option A and option B were implemented.	No	Not reported	1. HIV negative 2. Untreated HIV+ 3. ZDV initiated antenatal 4. TDF+FTC/3TC+ NVP, mixed initiation	PTB, LBW, SGA	LNMP
Rempis et al. 2017 [52]	Uganda	1	Retrospective cohort	February – December 2013	399	Women were recruited from a private hospital representing one of two referral hospitals of Kabarole District. The facility offers standard antenatal, delivery and HIV care. 10% of delivering women were HIV positive. Since September 2012, the facility implemented option B+ for PMTCT programme.	No	Not reported	1. HIV negative 2. TDF+3TC+EFV, mixed initiation	SGA	Finnstroem scoring system
Sebitloane et al. 2017 [53]	South Africa	1	Retrospective cohort	April 2011 – April 2014	1444	HIV-positive and HIV-negative women case records who delivered at King Edward VIII regional hospital (tertiary) were studied. HIV-positive women were older and had a higher parity than HIV-negative women.	No	Not reported	1. HIV negative 2. ZDV initiated antenatal 3. NNRTI-based HAART (EFV-based, NVP-based), mixed initiation	PTB	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Shapiro et al. 2010 [54]	Botswana	4	Prospective cohort	July 2006 – May 2008	709	The study analysed data from the Mma Bana study. Women were recruited from government run antenatal clinics in urban and rural communities.	Yes. A live-born and stillborn twin set was included in the live-born category.	HIV disease stage: not reported. CD4 cell count: median (IQR): 393 (305, 514) cells/μL.	1. ZDV+3TC+ABC initiated antenatal 2. ZDV+3TC+NVP initiated antenatal 3. ZDV+3TC+LPV/r initiated antenatal	PTB, VPTB, LBW, VLBW, MTCT	LNMP confirmed by ultrasound (early and late)
Silverman et al. 2010 [55]	Zambia	Not reported	Prospective cohort	Not reported	1143	Comparison group was recruited from the same location but at a time when HAART was not available.	Yes	Not reported	1. Untreated HIV+ 2. ZDV+3TC+LPV/r initiated antenatal	LBW	Not reported
The Kesho Bora Study Group et al. 2010 [56]	Burkina Faso, Kenya	3	Prospective cohort	January 2005 – September 2006	236	Participants recruited from antenatal clinics. Women treated with HAART were older and had a lower proportion of primigravidity than those treated with ZDV monotherapy. These two groups of women had similar profile with regards to education, occupation and marital status.	Yes. Only first born infants of multiple pregnancies included.	HIV disease stage: all women were on asymptomatic/early stage of HIV-1 disease (CD4 ≥500 cells/μL). CD4 cell count: median (IQR): 622 (559, 730) cells/μL.	1. ZDV initiated antenatal 2. ZDV+3TC+NVP initiated antenatal	PTB, LBW, MTCT	LNMP, SFH, ultrasound (unspecified)
van der Merwe et al. 2011 [57]	South Africa	2	Retrospective cohort	October 2004 – March 2007	1093	Women were recruited from HIV referral centres, including a tertiary hospital. 3.7% of women smoked and 3.9% consumed alcohol during pregnancy. 3.8% of women were diagnosed with a sexually transmitted disease (syphilis) during pregnancy.	No	WHO HIV stage: 16.7% to 78% of women were on stage 1, 7.6% to 16.7% stage 2, 7.4% to 61.1% stage 3, 1.1% to 16.7% stage 4. CD4 cell count: not reported.	1. Untreated HIV+ 2. d4T+3TC+NVP initiated antenatal 3. d4T+3TC+EFV initiated antenatal 4. d4T+3TC+LPV/r initiated antenatal	PTB, LBW, VLBW, SGA, MTCT	LNMP, SFH, ultrasound (unspecified) and neonatal assessment (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Wilkinson et al. 2015 [58]	Tanzania	Not reported	Prospective cohort	March 2012 – November 2012	100	Cohort was representative of HIV-positive pregnant women in Tanzania. Participants were recruited from rurally-located dispensaries and from Kisesa Health Centre.	No	Not reported	1. HIV negative 2. Any ART (ZDV monotherapy or ZDV+3TC+EFV, mixed initiation	PTB, LBW	LNMP, SFH
Zash et al. 2016 [59]	Botswana	2	Retrospective cohort	May 2009 – April 2011 and April 2013 – April 2014	7312	The study included women who delivered at the two largest public maternity wards in Botswana. These sites represent 25% of all births in the country.	Yes. Only first born infants of multiple pregnancies included.	HIV disease stage: not reported. CD4 cell count: median (IQR): from 222 (158, 349) to 475 (295, 586) cells/mm^3.	1. ZDV initiated antenatal 2. TDF+FTC+EFV, mixed initiation 3. Other HAART (NVP-based, LPV/r-based), mixed initiation	PTB, SGA, stillbirth	LNMP, SFH, ultrasound (unspecified)
Zash et al. 2017 [60]	Botswana	8	Retrospective cohort	August 2014 – August 2016.	44370	All women who delivered live-born or stillborn infants at 8 government maternity wards in Botswana were included in the study. These sites represent around 45% of all births in the country.	No	Not reported	1. HIV negative 2. HAART (EFV, NVP, or LPV/r-based), mixed initiation 3. Pre-conception TDF+FTC+EFV 4. Pre-conception TDF+FTC+NVP 5. Pre-conception ZDV+3TC+NVP 6. Pre-conception TDF+FTC+LPV/r 7. Pre-conception ZDV+3TC+LPV/r	PTB, VPTB, SGA, VSGA, stillbirth, NND	LNMP confirmed by ultrasound (unspecified) if available, or SFH

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Sub-Saharan Africa											
Zash et al. 2018 [61]	Botswana	8	Retrospective cohort	March 2013 – August 2016	3384	The study included birth-outcomes surveillance at 8 government maternity sites (the same study sites as Zash et al. 2017).	No	Not reported	1. Pre-conception TDF+FTC+EFV 2. TDF+FTC+EFV started 0-7 weeks 3. TDF+FTC+EFV started 8-13 weeks 4. TDF+FTC+EFV started 14-19 weeks 5. TDF+FTC+EFV started 20-21 weeks	PTB, VPTB, LBW, VLBW, SGA, VSGA, stillbirth, NND	LNMP confirmed by ultrasound (unspecified) if available, or SFH
Zash et al. IAS 2017 [26]	Botswana	8	Retrospective cohort	August 2014 – August 2016 and November 2016 – April 2017	5438	The study included all consecutive births ≥24 weeks' gestation at 8 maternity wards in Botswana (the same study sites as Zash et al. 2017 and Zash et al. 2018).	No	Not reported	1. DTG+TDF+FTC initiated antenatal 2. EFV+TDF+FTC initiated antenatal	PTB, VPTB, SGA, VSGA, stillbirth, NND	Not reported
Europe											
Boer et al. 2006 [62]	The Netherlands	1	Retrospective cohort	December 1997 – July 2003	339	HIV-positive women were recruited from an academic hospital, and HIV-negative women from an electronic database of women from the multicultural population living near the hospital.	Yes. Only first born infants of multiple pregnancies included.	Not reported	1. HIV negative 2. Non PI-based HAART, mixed initiation 3. PI-based HAART, mixed initiation	PTB, LBW, VLBW	LNMP and if needed was corrected by early ultrasound
European Collaborative study (ECS) et al. 2003 [63]	Belgium, Denmark, Germany, Italy, Netherlands Poland, Spain, Sweden, UK	26	Prospective cohort	1985 – December 2001	2414	Majority of black women included in the cohort were African born. 19.6% of women reported a history or current use of IV drugs.	Not reported	HIV disease stage: 13.7% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: not reported.	1. Untreated HIV+ 2. ZDV monotherapy 3. Non PI-based dual therapy, non PI-based HAART 4. PI-based HAART	PTB, LBW	LNMP, ultrasound (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Favarato et al. 2018 [64]	UK	Not reported	Retrospective cohort	2007 – 2015	6073	Women were mainly from sub-Saharan Africa (73.2%) with a median (IQR) age of 33 (29, 36) years. 50.9% of pregnancies were conceived on ART, whereas the remainder started ART on average at 19.1 (15.7, 22.1) weeks' gestation.	No	HIV disease stage: not reported. CD4 cell count: median (IQR): 456 (325, 610) cells/μL; distribution: 71.1% of women had a CD4 count >350 cells/μL, 28.9% ≤350 cells/μL.	1. EFV, or NVP-based HAART, mixed initiation 2. LPV/r-based HAART, mixed initiation 3. Other PI/r-based HAART, mixed initiation	PTB	Not reported
Favarato et al. IAS 2017 [65]	Ireland, UK	Not reported	Retrospective cohort	2007 – 2015	9951	The study used data reported to the National Study on HIV in Pregnancy and Childhood (NSHPC). 75.4% of mothers were born in Sub-Saharan Africa. 49.4% of pregnancies were conceived on ART.	No	HIV disease stage: not reported. CD4 cell count at 1st antenatal visit: distribution: among women with live births, 65.74% of women had a CD4 count >350cells/μL, 34.26% ≤350 cells/μL. Among women with stillbirths, 48.1% of women had a CD4 count >350 cells/μL, 51.9% ≤350 cells/ μL.	1. NNRTI-based ART, mixed initiation 2. PI/r-based ART, mixed initiation 3. INSTI-based ART mixed initiation 4. Other ART, mixed initiation 5. Any ART initiated preconception 6. Any ART initiated antenatal	Stillbirth	Not reported
Feiterna-Sperling et al. 2007 [66]	Germany	1	Prospective cohort	January 1997 – December 2004	215	Women were recruited from a tertiary multidisciplinary care center for HIV-positive women. 13.5% of women used illicit drugs (heroine, opiate, methadone, cocaine). All deliveries occurred at a healthcare facility.	Yes. Of the 221 babies, 6 pairs of twins were included.	CDC HIV disease stage: 12.2% of women were on stage C. CD4 cell count: not reported.	1. ZDV or ZDV+3TC dual, mixed initiation 2. HAART (NRTI, NNRTI, PI-based), mixed initiation	PTB, LBW	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Grignolo et al. 2017 [67]	Italy	2	Retrospective cohort	January 1985 – December 2014	262	The study population included women from the European Collaborative Study (ECS) and women excluded from the ECS.	Yes. Of 262 deliveries, four were twins.	Not reported	1. Untreated HIV+ 2. Any ART, mixed initiation 3. Monotherapy/dual mixed initiation 4. HAART, mixed initiation	VSGA	Not reported
Grosch-Woerner et al. 2008 [68]	Austria, Germany	13	Prospective cohort	1995 – 2001	183	Participants were recruited from health centres. All participants were offered an elective caesarean section, which would be performed at 36^{+0} weeks' gestation. 23.4% of women reported IV drug use during pregnancy. All deliveries occurred at a healthcare facility.	Yes. Only first born infants of multiple pregnancies included.	Not reported	1. Monotherapy (mostly ZDV), mixed initiation 2. Dual therapy (mostly ZDV+3TC), mixed initiation 3. HAART (NNRTI, PI-based), mixed initiation	LBW	LNMP
Hernandez et al. 2016 [69]	Spain	1	Prospective cohort	Not reported	51	The two treatment groups were matched byage and parity. Age ranged between 25 and 42 years. Alcohol and drug use were 0%.	No	HIV disease stage: all women were on asymptomatic stage. CD4 cell count: not reported.	1. HIV negative 2. HAART (NNRTI, PI-based), mixed initiation.	PTB, SGA	Not reported
Kowalska et al. 2003 [70]	Poland	1	Prospective cohort	January 1995 – February 2003	102	Women were recruited from an outpatient HIV clinic at a maternal and child health institute. 47.1% of women reported the use of illicit drugs during pregnancy.	Yes	HIV disease stage: across treatment groups, 6.4% to 16.7% of women were on AIDS stage (CD4 count <200 cells/μL). CD4 cell count: not reported.	1. Untreated HIV+ 2. ZDV monotherapy mixed initiation 3. Non PI-based HAART, mixed initiation 4. PI-based HAART, mixed initiation	PTB, LBW, MTCT	LNMP

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Lopez et al. 2012 [71]	Spain	1	Retrospective cohort	January 1986 – June 2010	1557	Women recruited from a tertiary hospital in an urban area. All deliveries were at the hospital. 55.2% of women smoked, and 1.4% used illicit drugs during pregnancy. 63.7% of women acquired HIV infection through heterosexual transmission, 55% through IV drug use and 0.8% through blood transfusions.	No	Not reported	1. HIV negative 2. Non HAART, mixed initiation 3. HAART (NRTI, NNRTI, PI-based), mixed initiation	PTB, sPTB, VPTB	Ultrasound (early second trimester)
Lopez et al. 2015 [72]	Spain	1	Prospective cohort	January 2006 – December 2011	156	Women recruited from a tertiary hospital in an urban area. 31.4% of women smoked, and 6.4% used illicit drugs during pregnancy.	No	HIV disease stage: 7.4% of women were on AIDS stage (CD4<200cells/μL). 1st trimester CD4 cell count: median (IQR): among women with SGA infants, 445.5 (25, 799) cells/μL. Among women with AGA infants, 448 (131, 1462) cells/μL.	1. HAART (NNRTI, PI-based), mixed initiation 2. NNRTI-based HAART, mixed initiation 3. PI-based HAART, mixed initiation	SGA	Ultrasound (1st trimester ultrasound or earliest available ultrasound in late gestation)
Mandelbrot et al. 1998 [73]	France	85	Retrospective cohort	September 1985 – December 1996	2819	Participants were recruited from obstetrical services. 40% women were originally from sub-Saharan Africa or the Carribean. 31% past or current IV drug use.	No	Not reported	1. Untreated HIV+ 2. ZDV monotherapy	PTB, MTCT	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Mandelbrot et al. 2001 [74]	France	85	Retrospective cohort	May 1994 – September 1998	1362	Participants recruited from obstetrical services. All women delivered at the hospitals.	Yes. Only first born infants of multiple pregnancies included.	HIV disease stage: not reported. CD4 cell count: median (range): among women treated with dual therapy, 426 (23, 1440)x10^6 cells/L; among women treated with monotherapy, 436 (0, 3502) x 10^6 cells/L.	1. ZDV monotherapy mixed initiation 2. ZDV+3TC, mixed initiation	PTB, SGA, MTCT	Not reported
Mandelbrot et al. 2015 [75]	France	90	Retrospective cohort	2000 – 2011	8678	71.6% of cohort were originally from sub-Saharan Africa and 16.6% were from metropolitan france. All women delivered at the hospitals.	Yes. Among 8678 infants, there were 218 twin pairs and one set of triplets.	Not reported	1. Any ART initiated preconception 2. Any ART initiated <14 weeks 3. Any ART initiated 14-27 weeks 4. Any ART initiated ≥28 weeks	PTB, VPTB, MTCT	LNMP and/or ultrasound (unspecified)
Montgomery – Taylor et al. 2015 [76]	UK	1	Retrospective cohort	January 2008 – December 2012	61	The study analysed data from an electronic hospital database and cross-referenced with databases held by the community HIV support team and genitourinary medicine department. 12.5% of women used alcohol, 3.3% of women smoked during pregnancy.	Not reported	HIV disease stage: not reported. CD4 cell count: median (IQR): among women who initiated ART preconception, 545 (355, 620) cells/mm^3; among those initiated ART antenatal, 350 (225, 525) cells/mm^3.	1. HAART (PI, non PI-based), mixed initiation 2. Non PI-based HAART, mixed initiation 3. PI-based HAART, mixed initiation	SGA	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Oomeer et al. 2015 [77]	UK	8	Retrospective cohort	October 2007 – October 2014	44	All women acquired HIV via heterosexual transmission. Median (IQR) of maternal age was 34 (23, 47) years. 83.6% of women were Black African.	Yes	HIV disease stage: 9.8% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: median (IQR): among women who initiated ART preconception, 430 (125, 1400) cells/μL; among those initiated ART antenatal, 341 (127, 713) cells/μL.	1. Pre-conception DRV/r-based ART 2. Antenatal DRV/r-based ART	PTB, LBW	Not reported
Rudin et al. 2011 [78]	Switzerland	Not reported	Prospective cohort	1984 – 2007	1180	The study was representative of HIV+ women in Switzerland. Median (IQR) of maternal age at birth: 29 (25, 33) years. 22% past or current tobacco smoking. Among 829 women (70% of total participants), 70% acquired HIV infection via sexual transmission, 26% IV drug use.	No	Not reported	1. Untreated HIV+ 2. ZDV monotherapy or dual therapy 3. HAART (non PI, PI-based), mixed initiation	PTB, VPTB	Not reported
Samuel et al. 2014 [79]	UK	12	Retrospective cohort	March 2004 – December 2010	99	Participants were recruited from HIV centres. 93.8% of women acquired HIV via heterosexual intercourse, 3.4% IV drug use, 2.1% MTCT and 0.7% blood transfusion.	No	HIV disease stage: not reported. CD4 cell count: median (range): 407 (15, 1161) cells/mm^3.	1. ATV-based HAART initiated preconception 2. ATV-based HAART initiated antenatal	PTB, LBW, MTCT	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Short et al. 2014 [18]	UK	1	Retrospective cohort	1996 – July 2010	331	Women were recruited from an HIV antenatal clinic. 13% current smokers. Less than 1% of women had a history of injecting drug use. 94% of women aquired HIV via heterosexual transmission. All women delivered at the healthcare facility.	Yes	HIV disease stage: 11.5% of women were on the stage of AIDS defining illness. CD4 cell count: median (IQR): 360 (227, 510) cells/μL.	1. Untreated HIV+ 2. Antenatal ZDV 3. NRTIs dual therapy, mixed initiation 4. ZDV+3TC+ABC initiated antenatal 5. NNRTI, PI-based HAART initiated antenatal 6. HAART initiated preconception 7. HAART initiated antenatal	PTB	Not reported
Sibiude et al. 2012 (main cohort) [80]	France	90	Retrospective cohort	1990 – 2009	11377	Women were recruited from obstetrics centers and all women delivered at the hospitals. 59.2% of women were originally from sub-Saharan Africa and 23.1% were originally from mainland France. 94.1% of women reported past or active use of IV drugs.	No	Not reported	1. Any ART initiated preconception 2. Any ART initiated antenatal 3. ZDV monotherapy mixed initiation 4. NRTIs dual therapy, mixed initiation 5. HAART (NNRTI-based, PI-based), mixed initiation	PTB	LNMP, corrected with ultrasound (early) if necessary
Sibiude et al. 2012 (substudy 1) [80]	France	Not reported	Prospective cohort	2005 – 2009	1253	Women were recruited from the largest maternity wards in France. All deliveries were at the hospitals. 87% women from sub-Saharan Africa, 11.6% from Europe. 1.5% past or active use of IV drugs. 5.5% current smoking.	No	CDC HIV stage: 96% of women were on stage A/B, 4% stage C. CD4 cell count: not reported.	1. Boosted PI-based HAART initiated antenatal 2. Non-boosted PI-based HAART initiated antenatal 3. PI-based HAART started <14 weeks 4. PI-based HAART started 14-20 weeks 5. PI-based HAART started 21-27 weeks 6. PI-based HAART started ≥28 weeks	PTB, VPTB	LNMP confirmed by ultrasound (early).

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Sibiude et al. 2012 (substudy 2) [80]	France	Not reported	Retrospective cohort	2000 – 2004	1094	Not reported	No	Not reported	1. Antenatal boosted PI-based HAART 2. Antenatal non-boosted PI-based HAART	PTB, VPTB	LNMP confirmed by ultrasound (early)
Snijdewind et al. 2018 [81]	The Netherlands	26	Retrospective cohort	1997 – 2015	9931	Only HIV+ women (≥18 years) who gave birth to HIV-exposed uninfected infants after a minimum of 24 weeks' pregnancy were eligible for the study. Women who started ART prior to conception had been receiving ART for a median (IQR) of 3.48 (2.08, 5.35) years.	No	Not reported	1. HIV negative 2. HAART, mixed initiation 3. NNRTI-based HAART, mixed initiation 4. PI-based HAART, mixed initiation	PTB, VPTB, LBW, VLBW, SGA	LNMP or 1st trimester ultrasound
Thorne et al. IAS 2017 [82]	Belgium, Germany, Ireland, Italy, Netherlands Spain, Switzerland, UK	Not reported	Retrospective cohort	Reported to the study by September 2016	79	Median (IQR) of maternal age at conception was 33.1 (26.7, 37.1) years and 54.3% of women born in sub-Saharan Africa. 83.8% of women acquired HIV infection via heterosexual transmission, 9 women were infected vertically and 3 had injecting drug use acquisition.	No	Not reported	1. DTG-based ART started 1st trimester 2. DTG-based ART started 2ndtrimester 3. DTG-based ART started 3rdtrimester	PTB, LBW, VLBW	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Townsend et al. 2007 (NSHPC) [83]	Ireland, UK	205	Prospective cohort	1990 – 2005	4939	The study was representative of HIV-positive women in the population. 20% of women who were on no treatment, 6.4% of women on monotherapy or dual therapy and 2.4% of women on HAART acquired HIV-infection via IV drug use. 63% of women who were on no treatment, 76.2% of women on monotherapy or dual therapy and 84.2% of women on HAART were originally from a high HIV prevalence area.	No	HIV disease stage: 8.5% to 13.8% of women were on symptomatic stage of HIV disease (AIDS); 6.1% to 15.3% of women had a CD4 count <200 cells/μL (AIDS). CD4 cell count: not reported.	1. Untreated HIV+ 2. Monotherapy or dual therapy, mixed initiation 3. HAART (NRTI, NNRTI, PI-based) started ≤12 weeks 4. HAART (NRTI, NNRTI, PI-based) started 13-26 weeks 5. NRTI-based HAART, mixed initiation 6. NNRTI-based HAART, mixed initiation 7. PI-based HAART, mixed initiation 8. PI/NNRTI-based HAART, mixed initiation	PTB, VPTB, stillbirth, NND	Not reported
Townsend et al. 2010 (ECS) [84]	Belgium, Denmark, Germany, Italy, Netherlands Poland, Spain, Sweden, UK	30	Prospective cohort	1990–2006	4253	98.7% of black women were born outside the study region, mainly in sub-Saharan Africa. 35.4% of women reported a history or current use of IV drugs.	No	HIV disease stage: 12.1% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: 12.1% of women had a CD4 count <200 cells/μL, 22.8% 200-349 cells/μL, 25.4% 350-499 cells/μL, 39.7% ≥500 cells/μL.	1. Untreated HIV+ 2. Monotherapy 3. Dual therapy (mostly ZDV+3TC) 4. HAART (non PI, PI-based)	PTB	LNMP, ultrasound (unspecified).

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Europe											
Townsend et al. 2010 (NSHPC) [84]	Ireland, UK	205	Prospective cohort	1990–2006	6426	97% of black women were born outside the study region, mainly in sub-Saharan Africa. 4.4% of cohort acquired HIV-infection through IV drug use.	No	HIV disease stage: 8% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: 12.9% of women had a CD4 count <200 cells/μL, 27.4% 200-349 cells/μL, 25.4% 350-499 cells/μL, 34.3% ≥500 cells/μL.	1. Untreated HIV+ 2. Monotherapy 3. Dual therapy (mostly ZDV+3TC) 4. HAART (non PI, PI-based)	PTB	Not reported
The Americas											
Aaron et al. 2012 [85]	USA	1	Prospective cohort	January 2000 – January 2011	183	Women were recruited from an urban medical clinic. 38.3% of women smoked, and 18% used illicit drugs during pregnancy.	Yes. Only first born infants of multiple pregnancies included.	HIV diseases stage: 26.8% of women were on AIDS stage (CD4≤200cells/μL). CD4 cell count: distribution: 26.8% of women had a CD4 count ≤200 cells/μL, 73.2% >200 cells/μL.	1. HAART, mixed initiation 2. NRTI-based HAART 3. NNRTI-based HAART 4. PI-based HAART	SGA, VSGA	Patients with sure LNMP in the 1st trimester were confirmed by a 2nd trimester ultrasound. Those with unsure LNMP, a 1st trimester ultrasound was used. Those presented after 1st trimester with unsure LNMP were dated by a 2nd or 3rd trimester ultrasound.

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Cooper et al. 2002 [86]	USA	Not reported	Prospective cohort	January 1990 – June 2000	1542	The cohort was representative of HIV-positive women in the US. Illicit drug use (heroin, opiates including methadone, cocaine, injecting drugs) was reported in 31% of women.	No	CDC HIV stage: 11.6% - 30.4% of women were on stage C. CD4 cell count: distribution: 48.4% - 58.4% of women had a CD4 count <500 cells/μL, 41.6% - 51.6% ≥500 cells/μL.	1. Untreated HIV+ 2. ZDV monotherapy 3. NRTIs or NNRTIs or NRTI+NNRTI dual therapy 4. HAART (NNRTI, PI-based)	PTB, LBW, MTCT	LNMP, SFH, ultrasound (unspecified), neonatal assessment (unspecified)
Cotter et al. 2006 [15]	USA	1	Prospective cohort	January 1990 – December 2002	1337	The cohort was representative of HIV-positive pregnant women in the US. 11.2% of women smoked, 5.4% consumed alcohol, 17.8% used illicit drugs and 39% were diagnosed with a sexually transmitted disease during pregnancy. All women delivered at the hospital.	No	CDC HIV stage: 64.4%-89.2% of women on stage A, 8.1%-23.2% stage B, 2.7%-20.5% stage C. 10.6%-41% women on AIDS stage (CD4<200cells/μL). CD4 cell count: not reported.	1. Untreated HIV+ 2. ZDV monotherapy mixed initiation 3. Non PI-based dual therapy or HAART, mixed initiation 4. PI-based dual therapy or HAART, mixed initiation	LBW, VLBW	LNMP confirmed by ultrasound (early and late)
Duryea et al. 2015 [87]	USA	1	Retrospective cohort	January 1984 – April 2014	1004	Women delivered at the institution of the University of Texas Southwestern Medical Center and Parkland Hospital, at which national treatment guidelines were implemented. Untreated HIV-positive women were more likely to be nulliparous than treated women.	No	HIV disease stage: not reported. CD4 cell count at antenatal-care presentation: median (IQR): among untreated HIV+, 557 (375, 747); women on non PI-based ART, 456 (314, 624); women on PI-based ART, 463 (299, 626) cells/mm^3.	1. Untreated HIV+ 2. Non PI-based ART 3. PI-based ART	PTB, SGA	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Einstein et al. 2004 [88]	USA	1	Retrospective cohort	August 2000 – May 2003	39	Women were recruited from an institutional database of high-risk obstetric patients. Maternal age was similar between the two treatment groups.	No	HIV disease stage: not reported. CD4 cell count: median (IQR): women treated with non PI-based ART, 487 (362); PI-based ART, 289 (354) cells/mL.	1. Non PI-based ART, mixed initiation 2. PI-based ART, mixed initiation	PTB, MTCT	LNMP, ultrasound (early)
Gagnon et al. 2016 [89]	Canada	1	Retrospective cohort	January 2007 – December 2012	384	All deliveries occurred at tertiary hospital. 84% of Black women were of African origin. 30% of HIV+ women were >35 years. 1% of HIV+ women used illicit drugs.	No	Not reported	1. HIV negative 2. Any ART	PTB, LBW, SGA	First trimester ultrasound or conception date by assisted reproduction
Haeri et al. 2009 [90]	USA	2	Retrospective cohort	January 2000 – January 2007	453	Women were recruited from two tertiary care centres. The women were predominantly from inner-city population.	Not reported	Not reported	1. HIV negative 2. HAART (non PI, PI-based)	PTB, sPTB, LBW, SGA	LNMP, ultrasound (unspecified)
Hofer et al. 2016 [91]	Brazil	1	Retrospective cohort	January 1996 – September 2010	428	The study analysed data from a tertiary pediatric hospital. Mothers of infants exposed to ART in the 1st trimester were slightly older than those exposed to ART in the 2nd/3rd trimester, or not exposed to ART. The median family income was US$ 592, corresponding to two minimum Brazilian wages of the year 2010.	No	HIV disease stage: not reported. CD4 cell count at first antenatal visit: median (IQR): untreated HIV+, 288 (205, 486); ART initiated preconception or 1st trimester, 371 (333, 525); 2nd or 3rd trimester, 444 (307, 597) cells/uL.	1. Untreated HIV+ 2. Any ART initiated preconception or in the 1st trimester 3. Any ART initiated in the 2nd/3rd trimester	PTB	Newborn examination (Capuro method)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Kakkar et al. 2015 [92]	Canada	1	Prospective cohort	1988 – 2011	589	Women were recruited from a tertiary referral centre and the largest maternal-health centre in the province.	No	HIV disease stage: 8.6%-11.9% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: not reported.	1. Untreated HIV+ 2. ZDV 3. NRTI, NNRTI-based ART 4. ZDV+3TC-based dual therapy or HAART 5. PI-based HAART (60.4% were non-boosted, 39.6% boosted). 6. Non PI-based HAART.	PTB	LNMP, ultrasound (unspecified)
Machado et al. 2009 [17]	Brazil	1	Prospective cohort	1996 – 2006	696	Participants were recruited from a HIV referral centre. 32.2% of women were diagnosed with a sexually transmitted disease during pregnancy. 9% of women used illicit drugs. 21.3% used tobacco during pregnancy.	No	CDC HIV stage: among women who initiated treatment preconception, 33.7% of women were on stage B/C; among women who initiated treatment antenatal, 10.2% were on stage B/C. CD4 cell count: distribution: among women who initiated treatment preconception, 17.1% had CD4 <200 cells/ μL; among women who initiated treatment antenatal, 14% had CD4 <200 cells/μL.	1. Any ART, mixed initiation 2. Antenatal ZDV 3. NTRIs dual therapy, mixed initiation 4. HAART, mixed initiation 5. NNRTI-based HAART, mixed initiation 6. PI-based HAART, mixed initiation	PTB, LBW	LNMP, ultrasound (earliest available)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Mounce et al. 2017 [29]	USA	1	Retrospective cohort	January 2007 – May 2015	19	Women were recruited from a single HIV clinic. Median (IQR) of maternal age at delivery was 31 (26, 35) years.	Not reported	Not reported	1. DTG, EVG or RAL-based HAART, mixed initiation 2. LPV/r or ATV/r-based HAART, mixed initiation	LBW, MTCT	Not reported
Papp et al. 2015 [93]	Canada	4	Prospective cohort	September 2010 – May 2013	44	A large proportion of the participants were born in Africa or the Caribbean. None were current tobacco smokers. Women were >18 years at enrolment.	No	Not reported	1. HIV negative 2. HAART (NNRTI, PI-based), mixed initiation	sPTB, SGA	LNMP confirmed by ultrasound (unspecified)
Patel et al. 2010 [94]	Puerto Rico, USA	56	Retrospective cohort	October 2002 – March 2008	777	The study population included women enrolled in the International Maternal Pediatric Adolescent AIDS Clinical Trials Group. 55% women diagnosed with HIV prior to conception, and 13% had a history of PTB. Comorbid diagnoses during pregnancy: gestational diabetes (1%), gestational hypertension (3%), hepatitis C infection (4%), and sexually transmitted infections (19%).	No	CDC HIV stage: 92% of women were on stage N/A/B, 8% stage C. CD4 cell count: not reported.	1. Antenatal non PI-based ART 2. Antenatal PI-based HAART	PTB, sPTB, VPTB	LNMP confirmed by ultrasound (unspecified), maternal physical exam (unspecified), conception date by assisted reproduction

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Phiri et al. 2015 [95]	USA	Not reported	Retrospective cohort	January 1994 – December 2009	604	Women were recruited from a source population of women enrolled in the Tennessee Medicaid (TennCare) database. 6.7% of women used alcohol, 25% used tobacco and 11% used illicit drugs during pregnancy.	No	HIV disease stage: 17.2% of untreated and 54.6% of treated HIV+ women were on AIDS stage.	1. Untreated HIV+ 2. Monotherapy NRTI, mixed initiation 3. NRTI-based dual therapy/HAART mixed initiation 4. NNRTI+NRTI dual therapy, mixed initiation 5. PI-based ART, mixed initiation	PTB, VPTB, LBW, VLBW, SGA	LNMP, clinical assessment (unspecified), ultrasound (unspecified)
Ransom et al. 2013 [96]	Puerto Rico, USA	56	Retrospective cohort	October 2002 – September 2011	630	Participants were recruited from clinical sites. 22% of women smoked during pregnancy.	No	HIV disease stage: 15% of women were on AIDS stage with CD4 <200 cells/mm^3, 18% on AIDS stage – CDC stage C. CD4 cell count: distribution: 15% of women had a CD4 count <200, 22% 200-349, 62% ≥350 cells/mm^3.	1. TDF-based HAART initiated in the 1st trimester 2. TDF-based HAART initiated in 2nd/3rd trimester	SGA	LNMP confirmed by ultrasound (unspecified), maternal physical exam unspecified), conception date by assisted reproduction
Schulte et al. 2007 [97]	USA	8	Retrospective cohort	1989 – 2004	8793	One third of mothers used illicit drugs. 7% of mothers had symptomatic HIV disease at delivery.	Not reported	HIV disease stage: 7.3% and 92.7% of women were on symptomatic and asymptomatic stage, respectively.	1. Untreated HIV+ 2. Monotherapy 3. Dual therapy 4. Non PI-based HAART 5. PI-based HAART	PTB, LBW	LNMP, ultrasound (unspecified) and neonatal assessment (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Simonds et al. 1998 [98]	USA	4	Retrospective cohort	1985 – December 1995	1032	The median age of enrolled women was 29 years. 64% of women were black, 25% Hispanic and 7% white.	No	HIV disease stage: 11% of untreated and 21% of treated HIV+ were on CDC stage C. 11% of entire cohort were on AIDS stage with a CD4 count <200 x 10^6 cells/L. CD4 cell count: median: 527 x 10^6 cells/L.	1. Untreated HIV+ 2. ZDV monotherapy	PTB, LBW	Not reported
Szyld et al. 2006 [99]	Argentina, Bahamas, Brazil, Mexico	Not reported	Prospective cohort	September 2002 – March 2005	681	Women recruited from pre-existing outpatient clinics for HIV-1 infected pregnant women. 9.4% of women consumed alcohol, 21.4% used tobacco, 2.3% used illicit drugs, 2.1% used marijuana during pregnancy. 5.9% of women were diagnosed with a sexually transmitted disease during pregnancy.	No	CDC HIV stage: 85.8% of women were on stage A, 6% stage B, 8.2% stage C; 13.2% were on AIDS stage (CD4<200cells/μL). CD4 cell count: distribution: 13.2% of women had s CD4 count <200, 55.3% 200-499, 31.5% ≥500 cells/μL.	1. NRTI-based monotherapy or dual therapy, mixed initiation 2. NNRTI-based HAART, mixed initiation 3. PI-based HAART, mixed initiation	PTB, LBW	LNMP with or without ultrasound (unspecified), neonatal assessment (unspecified)
Townsend et al. 2010 (PSD) [84]	Puerto Rico, USA	8	Retrospective cohort	1990–2004	8667	83.3% of black women were born in the study region. 13% of women reported a history of intravenous drug use. 36.2% of women delivered by cesarean section.	No	HIV diseases stage: 13.2% of women were on AIDS stage (CD4<200cells/μL). CD4 cell count: not reported.	1. Untreated HIV+ 1. Monotherapy 2. Dual therapy 3. HAART	PTB	LNMP, ultrasound, or neonatal assessment (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
The Americas											
Watts et al. 2013 [100]	Puerto Rico, USA	Multicentre (unspecified)	Retrospective cohort	2007 – 2009 and 2007 – October 2010	1869	Median (IQR) of maternal age was 27 (23, 32) years. 65% of women were Black, 28% white and 7% other/unknown. 34% of women had less than high-school education. 19% of women were diagnosed with a genital infection. 8% of women consumed alcohol, 17% smoked and 8% used illicit drug during pregnancy.	No	Not reported	1. Untreated HIV+ 2. Monotherapy or dual therapy 3. NRTI-based HAART, mixed initiation 4. NNRTI-based HAART, mixed initiation 5. PI-based HAART, mixed initiation	PTB, sPTB, SGA	Clinical assessment and ultrasound (unspecified)
Williams et al. 2013 [101]	USA	1	Retrospective cohort	July 2000 – November 2007	188	The study analysed data from an electronic database. All women delivered at the hospital. 38% of women used tobacco, 25% used illicit drugs during pregnancy	No	HIV disease stage: not reported. CD4 cell count: mean±SD: among women treated with non PI-based HAART, 593.3±270.5; among women treated with PI-based HAART, 377.1±224 cells/mm^3.	1. Non PI-based HAART, mixed initiation 2. PI-based HAART, mixed initiation	PTB	LNMP if consistent with clinical assessment and sonogram, or by sonogram if the LNMP was unknown
Asia											
Ai-jie et al. 2013 [102]	China	5	Retrospective cohort	January 2006 – March 2008	156	Women were recruited from counties (districts and cities) with a moderate to high HIV-epidemic.	Yes. One set of twins included.	HIV disease stage: not reported. CD4 cell count: distribution: 23.7% of women had a CD4 count <250, 76.3% ≥250 cells/μL.	1. Untreated HIV+ 2. ZDV monotherapy 3. ZDV+3TC+NVP	LBW	Not reported

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Asia											
Chakornbandit et al. 2015 [103]	Thailand	1	Retrospective cohort	January 2002 – December 2013	166	The study analysed data from a hospital database. Mean±SD of maternal age was 28±5.2 years. 36.1% of women were nulliparous, and 8.4% were diagnosed with gestational diabetes.	No	HIV disease stage: not reported. CD4 cell count: mean±SD: women treated with ZDV, 395.3±181.1; with PI-based HAART, 409.2±189.5 cells/mm^3.	1. ZDV monotherapy initiated antenatal 2. PI-based HAART initiated antenatal	sPTB	LNMP, ultrasound (early or late)
Darak et al. 2013 [104]	India	50	Prospective cohort	January 2008 – March 2012	495	Women were recruited from an area with a high HIV prevalence. 17% of women reported past opportunistic infections. 13% of women had symptoms of a sexually transmitted disease during pregnancy.	No	HIV disease stage: 1% of women treated with ZDV and 28.7% with HAART were on AIDS stage (CD4<200cells/µL). CD4 cell count: distribution: women treated with ZDV, 1% had CD4 <200, 11.9% 200-350, 35.7% 350-500, 51.4% >500; with HAART, 28.7% had CD4 <200, 46.6% 200-350, 11.2% 350-500, 13.5% >500 cells/µL.	1. ZDV monotherapy initiated antenatal 2. HAART (NNRTI, PI-based), mixed initiation.	PTB, LBW	LNMP or ultrasound (unspecified)

Table 3.1 Characteristics of studies included in the systematic review (*continued from previous page*).

Study	Country	Number of sites	Study design	Recruitment time period	Number of pregnant women/ pregnancies analysed	Population characteristics	Twin pregnancies included	HIV disease stage and CD4 cell count at enrolment	Antenatal treatments	Perinatal outcomes	Gestational age estimation methods
Multi-regions											
Vannappagari et al. IAS 2017 [27]	Argentina, Australia, Brazil, Canada, Ethiopia, Israel, Puerto Rico, Russia, UK, USA	Not reported	Prospective cohort	Reported to the study by January 2016	119	The study used data from the Antiretroviral Pregnancy Registry. Median (range) of maternal age was 29 (16, 42) years. 62% of women were Black, 14.1% white, 3.5% Asian, 17.6% Hispanic, 0.7% other ethnicity.	No	HIV disease stage: not reported. CD4 cell count: distribution: 26.2% of women had a CD4 count <200, 31.1% 200-499, 37.7% ≥500 cells/ μL, 4.9% with an unknown CD4 count.	1. DTG-based ART initiated in the 1st trimester 2. DTG-based ART initiated in the 2nd/3rd trimester	PTB, LBW, VLBW	Not reported

Abbreviations: ABC, abacavir; AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; ATV, atazanavir; ATV/r, atazanavir/ritonavir; BMI, body mass index; CDC, Centers for Disease Control and Prevention; d4T, stavudine; DRV/r, darunavir/ritonavir; DTG, dolutegravir; ECS, European Collaborative Study; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; HAART, highly active antiretroviral; therapy; HIV, human immunodeficiency virus; IAS, International AIDS Society; INSTI, integrase strand transfer inhibitor; IQR, inter-quartile range; IV, intravenous; LBW, low birth weight; LNMP, last normal menstrual period; LPV/r, lopinavir/ritonavir; MTCT, mother-to-child transmission; NND, neonatal death; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NSHPC, National Study on HIV in Pregnancy and Childhood; NVP, nevirapine; PI, protease inhibitor; PI/r, protease inhibitor/ritonavir; PMTCT, prevention of mother-to-child transmission; PSD, Pediatric Spectrum of HIV Disease; PTB, preterm birth; RAL, raltegravir; SD, standard deviation; SFH, symphysis-fundal height; SGA, small for gestational age; sPTB, spontaneous preterm birth; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; UK, United Kingdom; USA, United States of America; VLBW, very low birth weight; VPTB, very preterm birth; VSGA, very small for gestational age; WHO, world health organization; ZDV, zidovudine.

Appendix 3.7

Sensitivity analyses and summary of meta-analysis results: effect of maternal HIV/ART on adverse perinatal outcomes.

Preterm birth

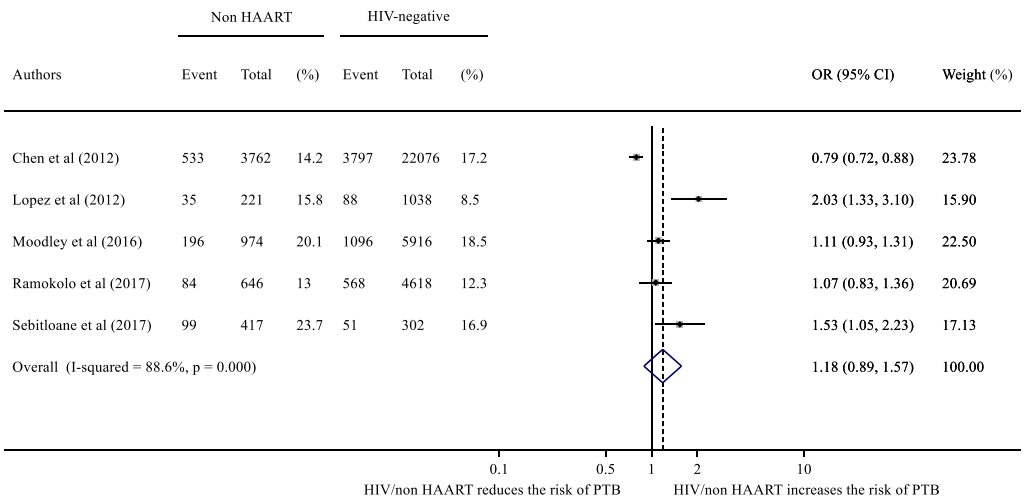


Figure 3.1. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with non HAART versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

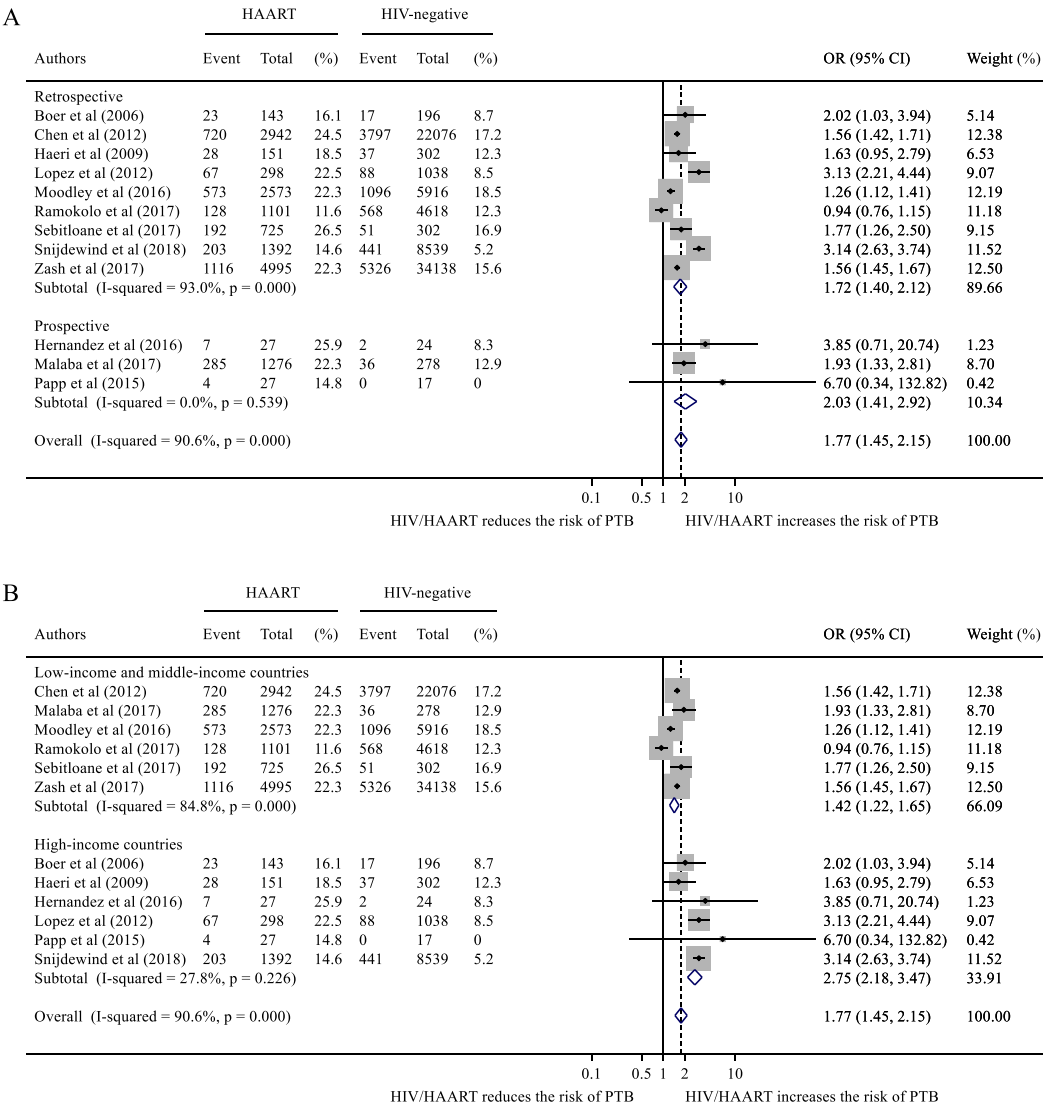


Figure 3.2. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

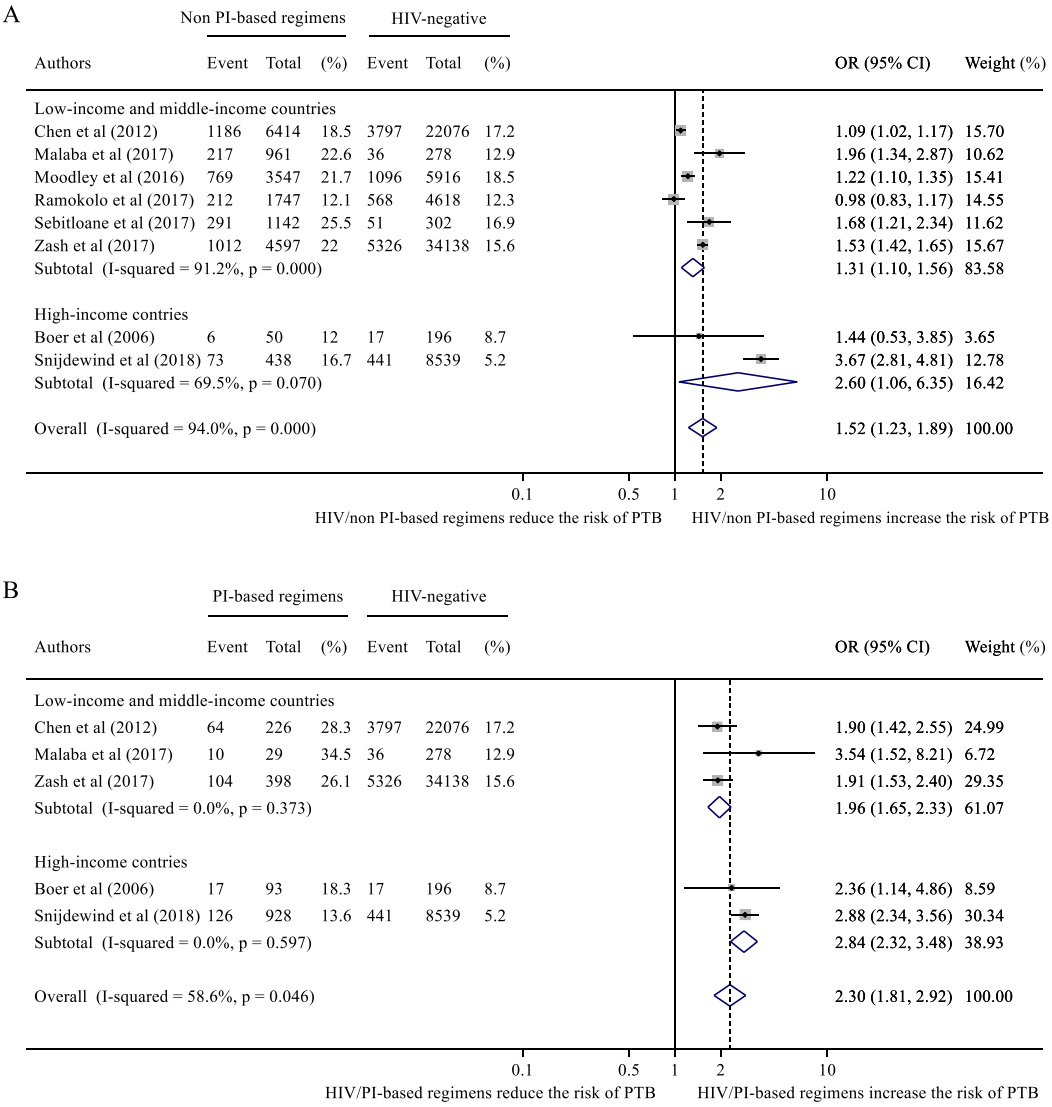
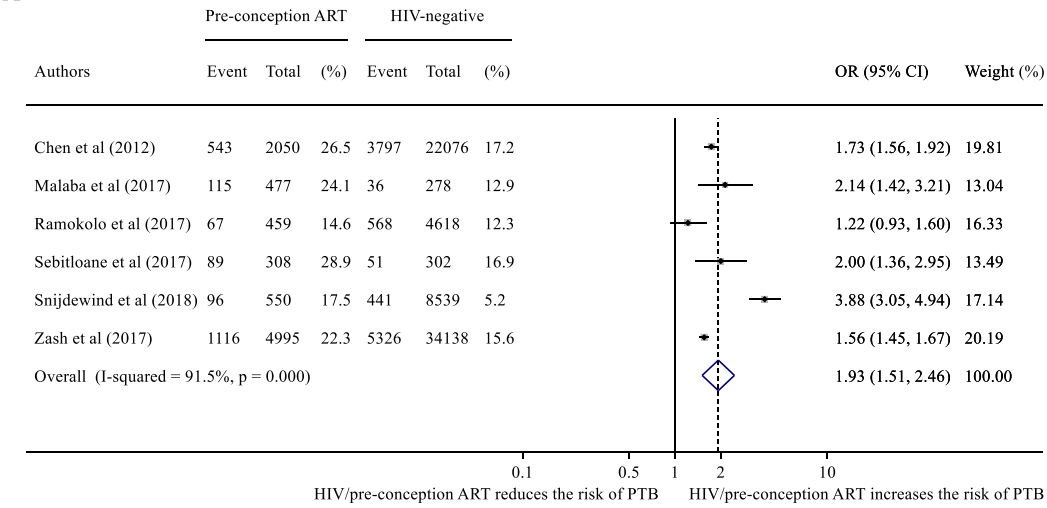


Figure 3.3. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non PI (A) and PI-based regimens (B) versus HIV-negative pregnant women using unadjusted data, by country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

A



B

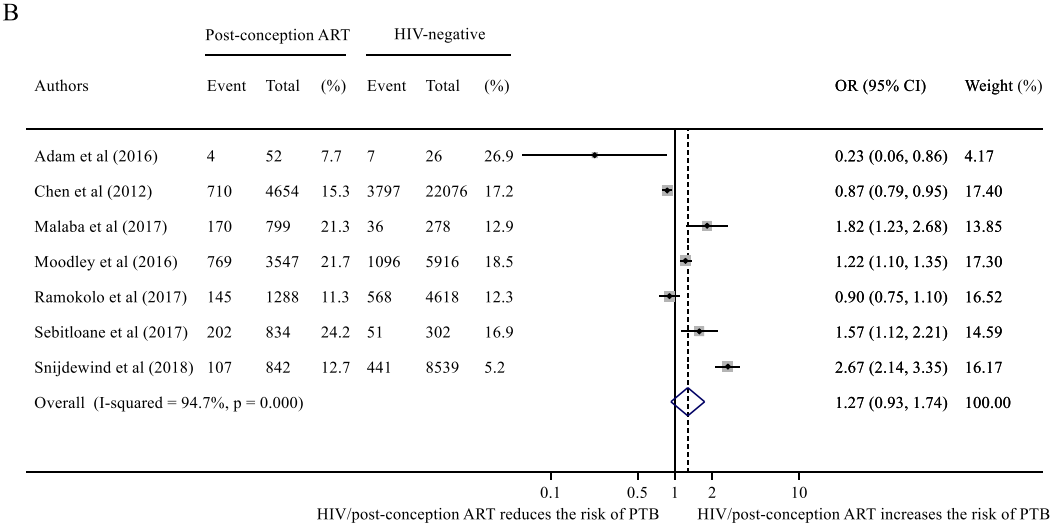


Figure 3.4. Forest plots of risk of preterm birth in treated HIV-positive pregnant women who initiated ART pre-conception (A) or post-conception (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Low birth weight

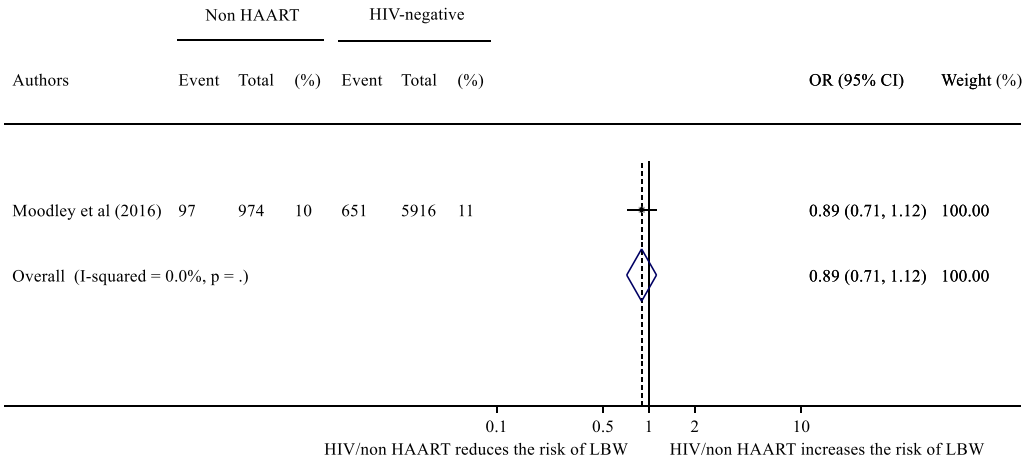


Figure 3.5. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with non HAART versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

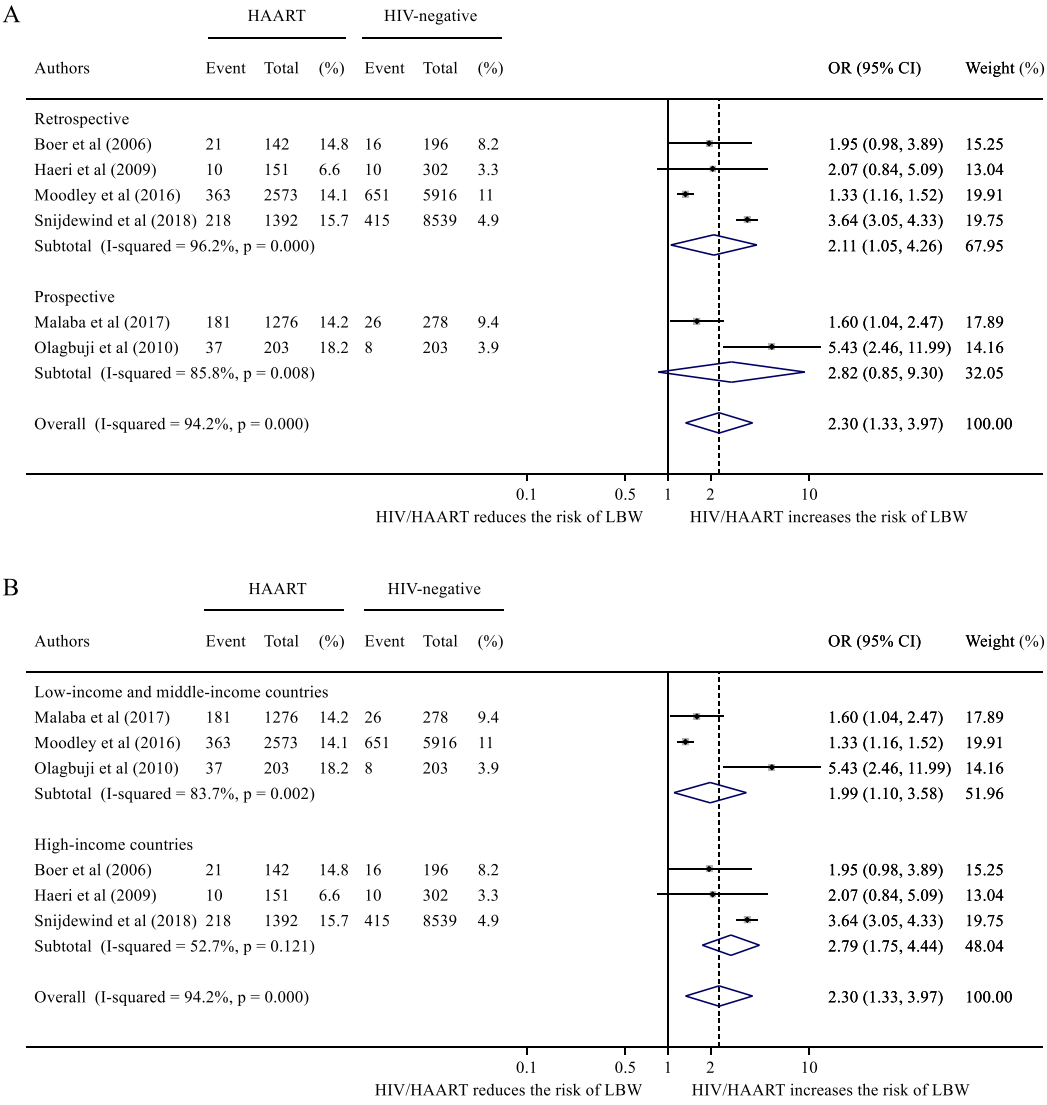


Figure 3.6. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with HAART versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

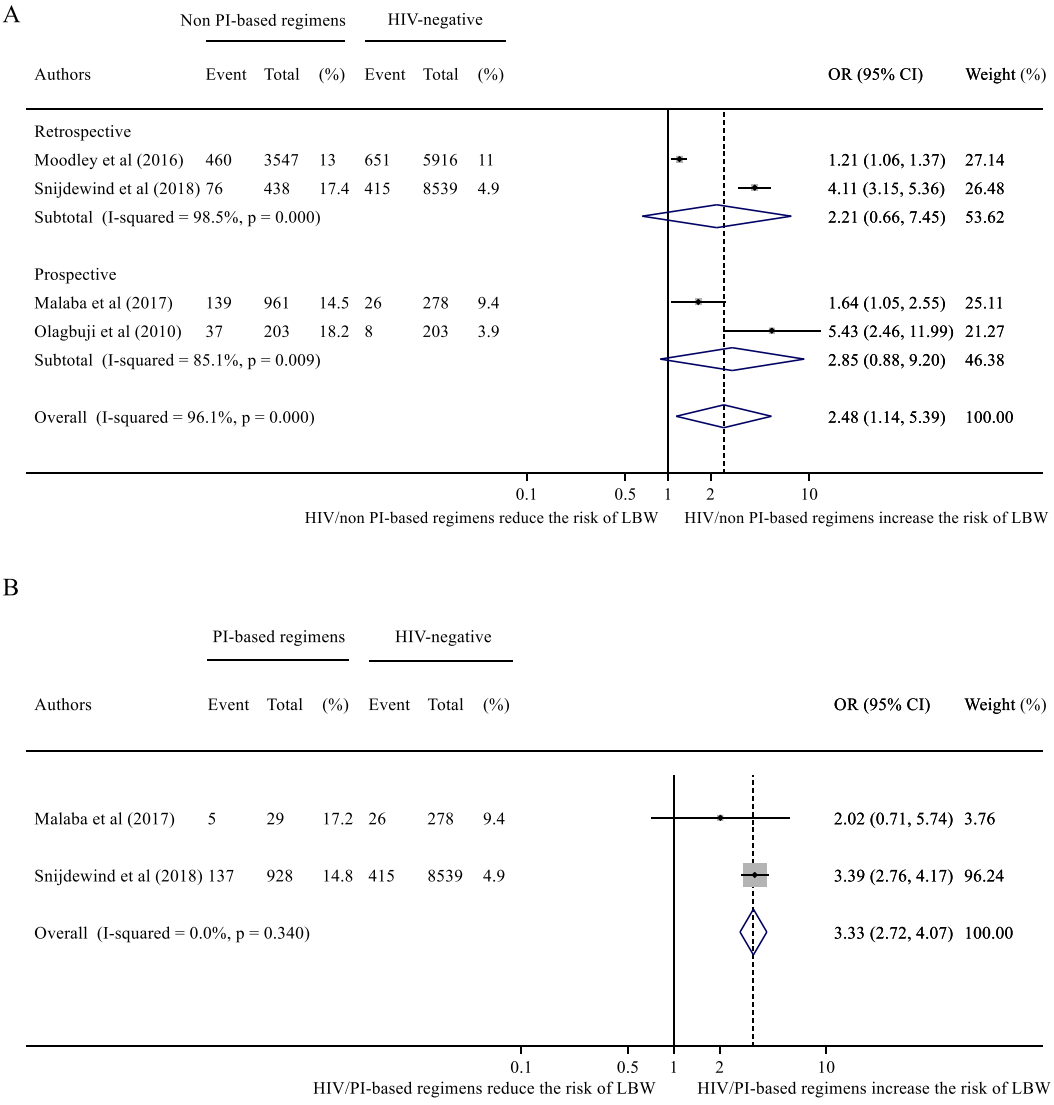
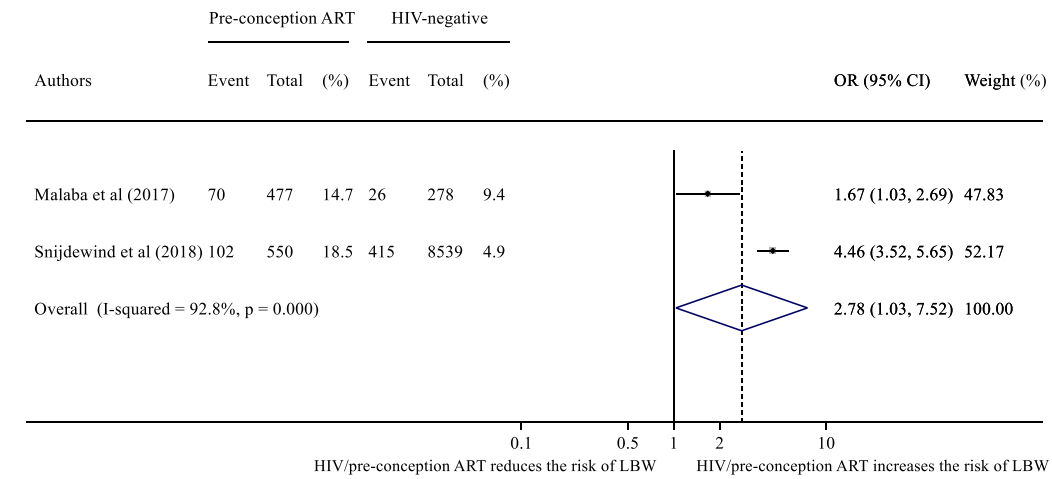


Figure 3.7. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non PI (A) or PI-based regimens (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

A



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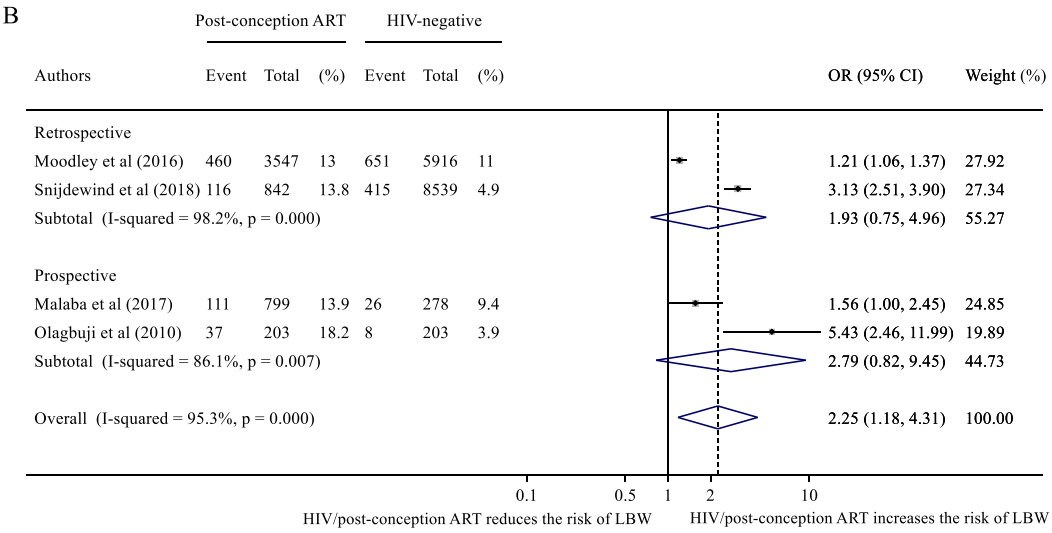
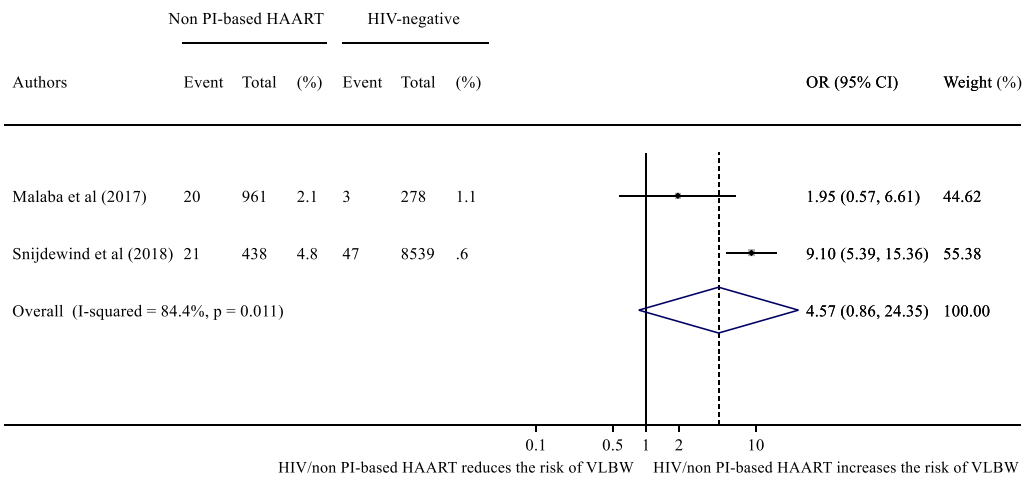


Figure 3.8. Forest plots of risk of low birth weight in treated HIV-positive pregnant women who initiated ART pre-conception (A) and post-conception (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

Very low birth weight

A



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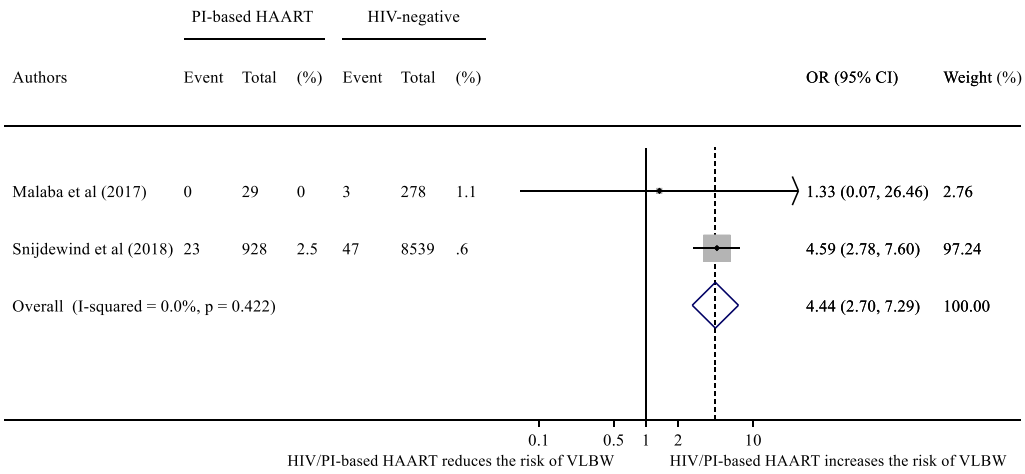
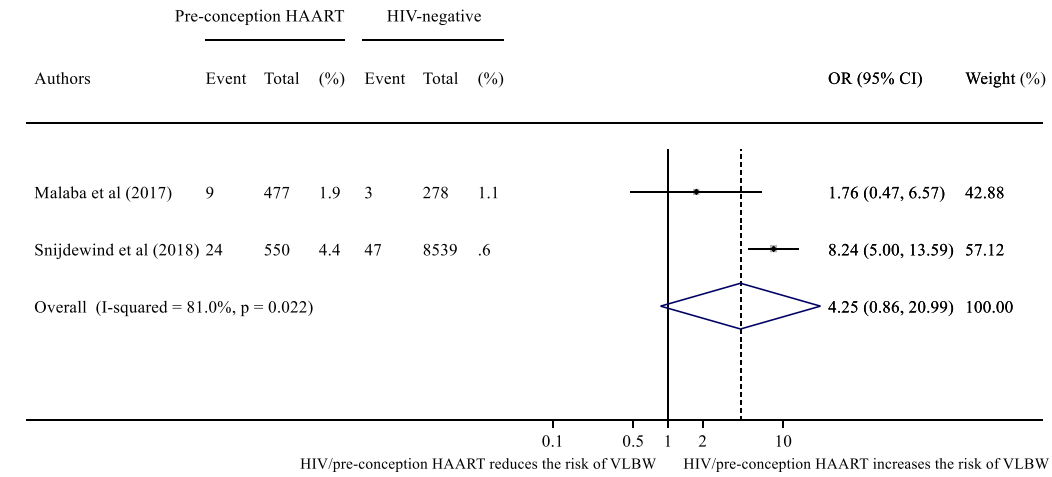


Figure 3.9. Forest plots of risk of very low birth weight in HIV-positive pregnant women treated with non PI (A) or PI-based regimens (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highliy active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; VLBW, very low birth weight.

A



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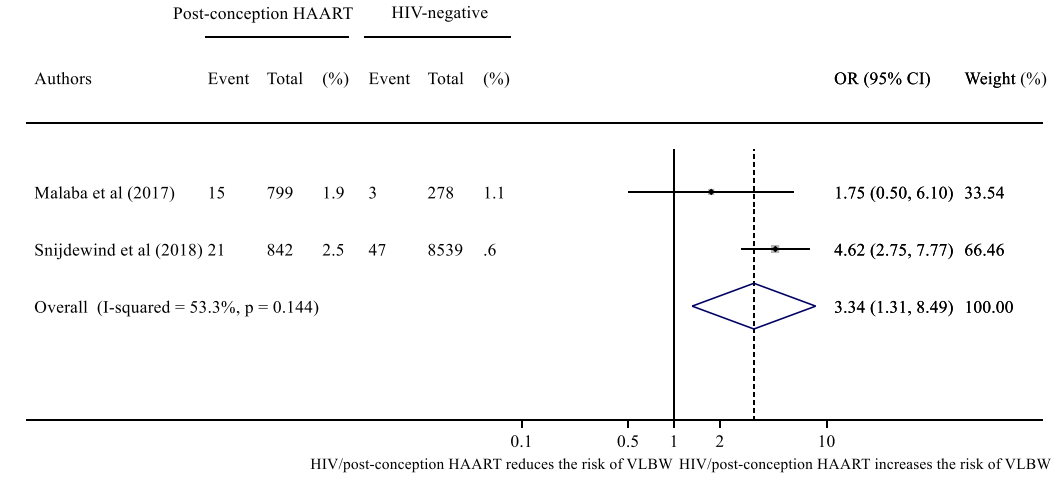


Figure 3.10. Forest plots of risk of very low birth weight in treated HIV-positive pregnant women who initiated ART pre-conception (A) or post-conception (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VLBW, very low birth weight.

Small for gestational age

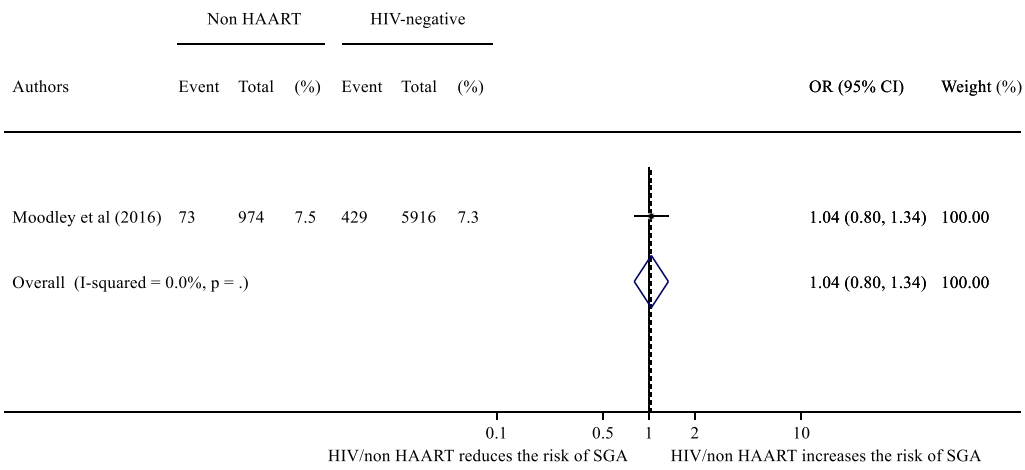


Figure 3.11. Forest plot of risk of small for gestational age in HIV-positive pregnant women treated with non HAART versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

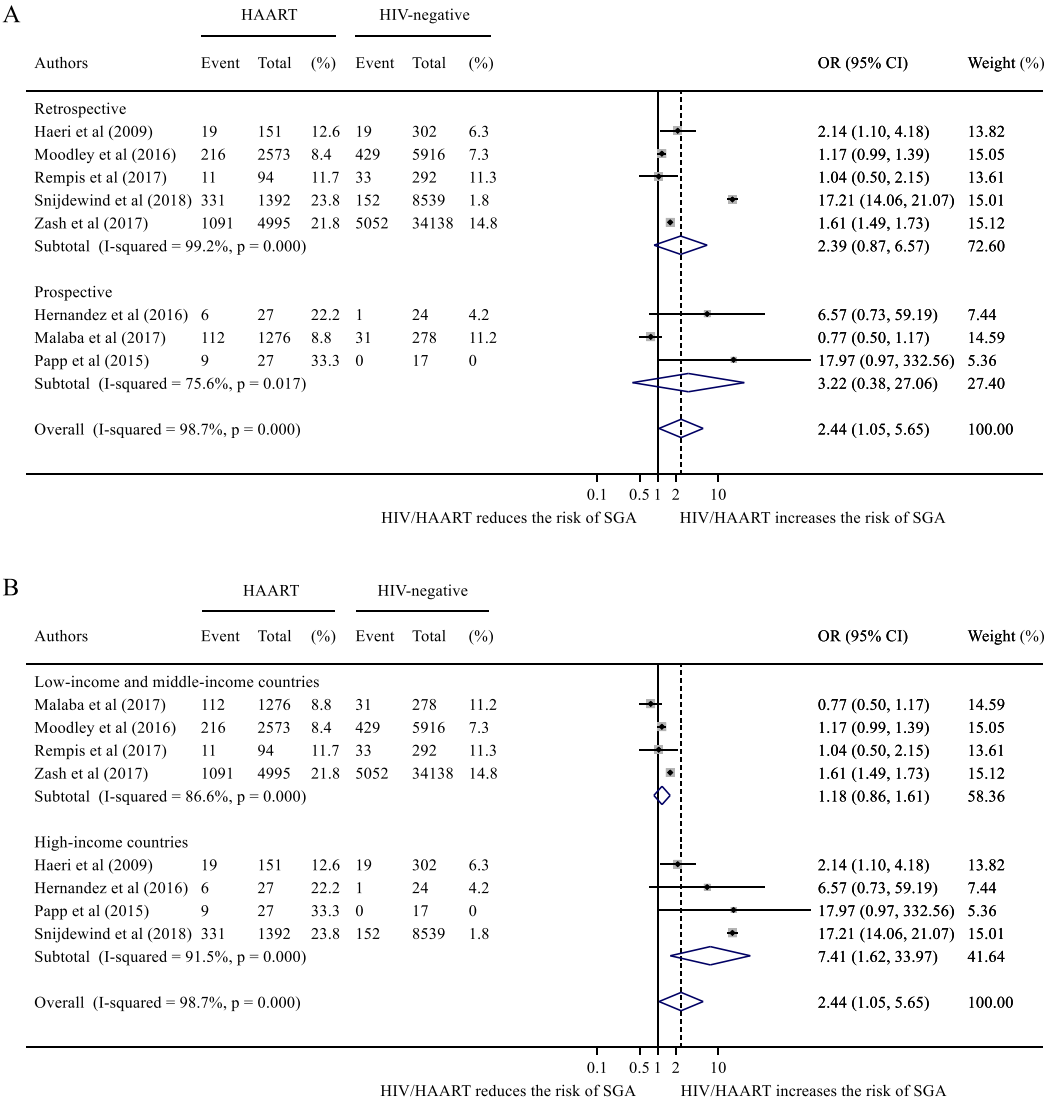
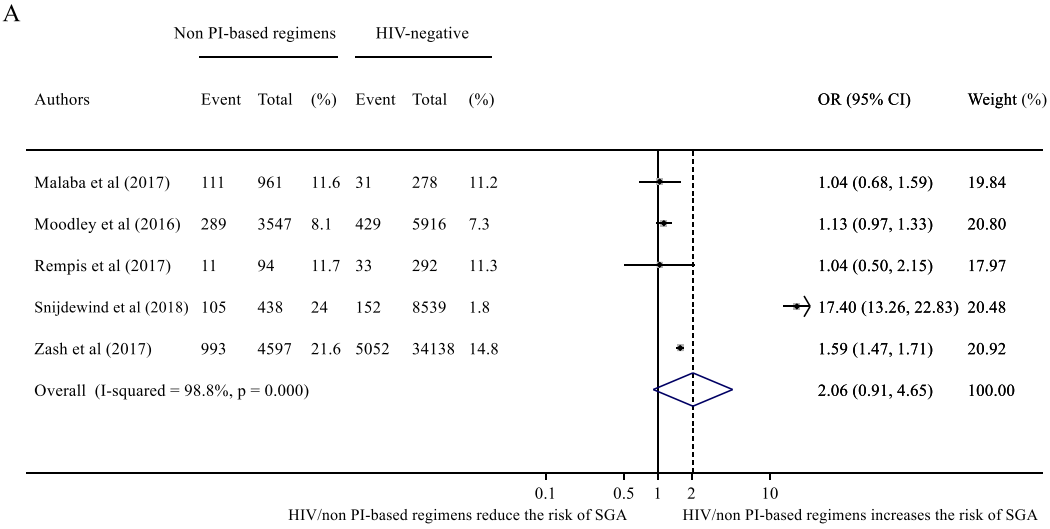


Figure 3.12. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with HAART versus HIV-negative pregnant women using unadjusted data, by cohort design (A) and country-income status. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

A



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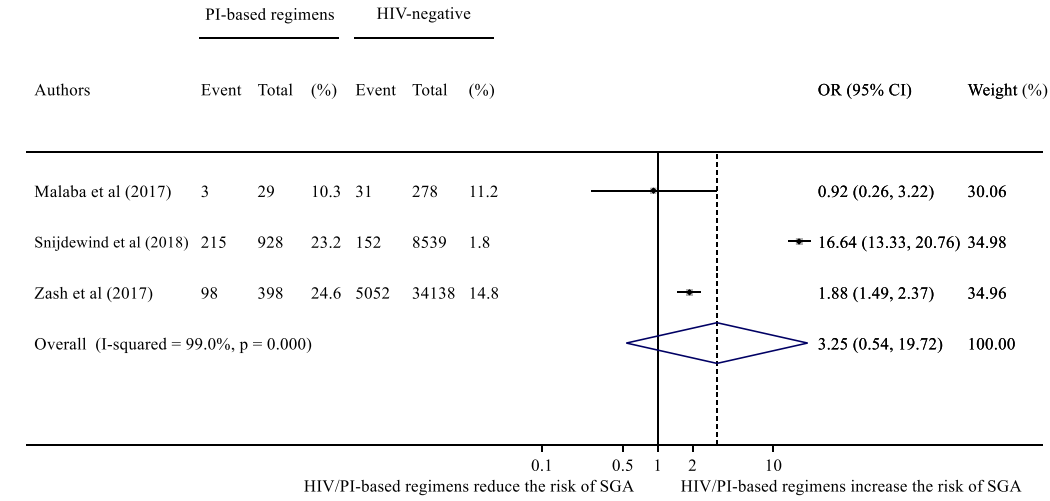
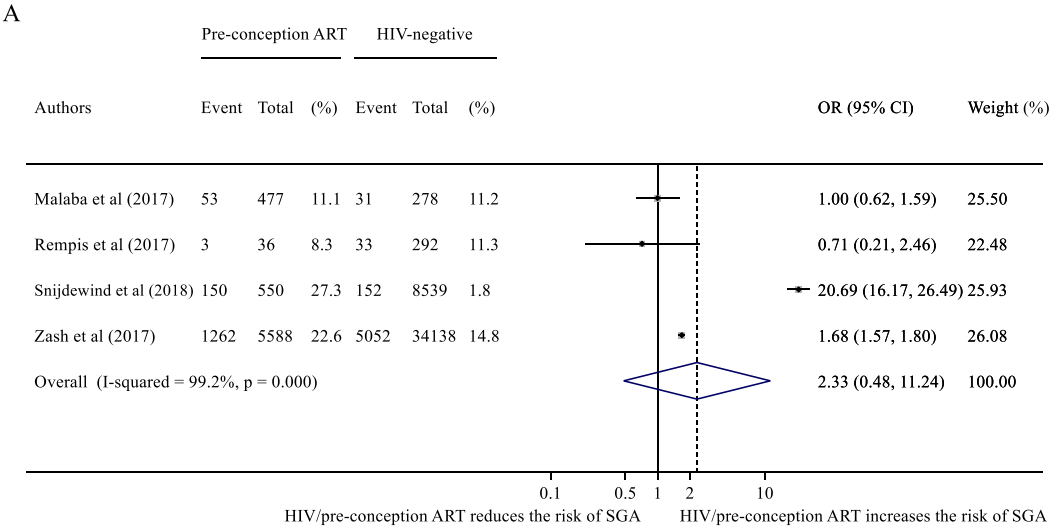


Figure 3.13. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with non PI (A) or PI-based regimens (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

A



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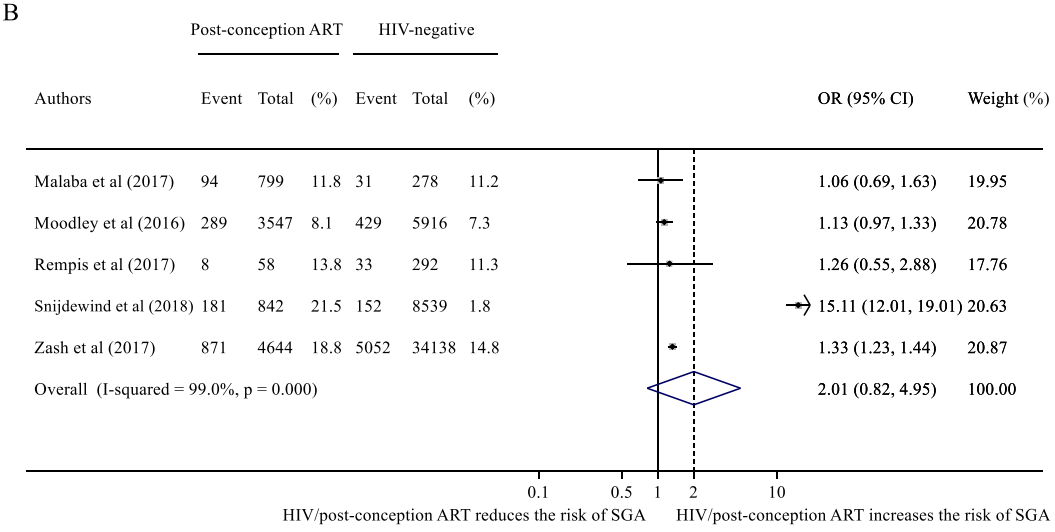


Figure 3.14. Forest plots of risk of small for gestational age in treated HIV-positive pregnant women who initiated ART pre-conception (A) or post-conception (B) versus HIV-negative pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

Table 3.2. Summary of meta-analysis results for the effect of maternal HIV/ART on perinatal outcomes using unadjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Treated HIV-positive (any ART) versus HIV-negative	PTB	15	1.63 (1.33, 2.01)	92.5	11	1.59 (1.27, 1.98)	94.5	4	1.92 (1.37, 2.68)	0	8	1.29 (1.08, 1.54)	89.7	7	2.68 (2.23, 3.23)	16.4
	sPTB	3	2.27 (1.68, 3.06)	0												
	VPTB	4	2.59 (1.15, 5.80)	91.4							2	1.43 (0.96, 2.14)	12.8	2	3.69 (1.93, 7.04)	64.8
	LBW	8	2.30 (1.36, 3.90)	93.7	5	2.19 (1.11, 4.32)	96.1	3	2.55 (0.98, 6.66)	71.9	4	1.90 (1.05, 3.43)	79.7	4	2.99 (2.17, 4.13)	31.6
	SGA	9	2.45 (1.15, 5.21)	98.5	6	2.44 (1.01, 5.89)	99	3	3.22 (0.38, 27.06)	75.6	4	1.18 (0.86, 1.62)	88.5	5	5.68 (1.54, 20.99)	93.6
	VSGA	1	1.90 (1.71, 2.11)	–												
	Stillbirth	1	1.74 (1.48, 2.06)	–												
	NND	1	1.17 (0.97, 1.41)	–												
Non HAART versus HIV-negative	PTB	5	1.18 (0.89, 1.57)	88.6												
	LBW	1	0.89 (0.71, 1.12)	–												
	SGA	1	1.04 (0.80, 1.34)	–												
HAART versus HIV-negative	PTB	12	1.77 (1.45, 2.15)	90.6	9	1.72 (1.40, 2.12)	93	3	2.03 (1.41, 2.92)	0	6	1.42 (1.22, 1.65)	84.8	6	2.75 (2.18, 3.47)	27.8
	LBW	6	2.30 (1.33, 3.97)	94.2	4	2.11 (1.05, 4.26)	96.2	2	2.82 (0.85, 9.30)	85.8	3	1.99 (1.10, 3.58)	83.7	3	2.79 (1.75, 4.44)	52.7
	VLBW	3	1.96 (0.42, 9.04)	84.4												
	SGA	8	2.44 (1.05, 5.65)	98.7	5	2.39 (0.87, 6.57)	99.2	3	3.22 (0.38, 27.06)	75.6	4	1.18 (0.86, 1.61)	86.6	4	7.41 (1.62, 33.97)	91.5

Table 3.2. Summary of meta-analysis results for the effect of maternal HIV/ART on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Non PI-based regimens versus HIV-negative	PTB	8	1.52 (1.23, 1.89)	94							6	1.31 (1.10, 1.56)	91.2	2	2.60 (1.06, 6.35)	69.5
	LBW	4	2.48 (1.14, 5.39)	96.1	2	2.21 (0.66, 7.45)	98.5	2	2.85 (0.88, 9.20)	85.1						
	VLBW	2	4.57 (0.86, 24.35)	84.4												
	SGA	5	2.06 (0.91, 4.65)	98.8												
PI-based regimens versus HIV-negative	PTB	5	2.30 (1.81, 2.92)	58.6							3	1.96 (1.65, 2.33)	0	2	2.84 (2.32, 3.48)	0
	LBW	2	3.33 (2.72, 4.07)	0												
	VLBW	2	4.44 (2.70, 7.29)	0												
	SGA	3	3.25 (0.54, 19.72)	99												
Pre-conception ART versus HIV-negative	PTB	6	1.93 (1.51, 2.46)	91.5												
	LBW	2	2.78 (1.03, 7.52)	92.8												
	VLBW	2	4.25 (0.86, 20.99)	81												
	SGA	4	2.33 (0.48, 11.24)	99.2												
Post-conception ART versus HIV-negative	PTB	7	1.27 (0.93, 1.74)	94.7												
	LBW	4	2.25 (1.18, 4.31)	95.3	2	1.93 (0.75, 4.96)	98.2	2	2.79 (0.82, 9.45)	86.1						
	VLBW	2	3.34 (1.31, 8.49)	53.3												
	SGA	5	2.01 (0.82, 4.95)	99												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; NND, neonatal death; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Table 3.3. Summary of meta-analysis results for the effect of maternal HIV/ART on perinatal outcomes using adjusted effect estimates.

ART comparison	Perinatal outcomes	Overall meta-analysis		
		N	OR (95% CI)	I^2 (%)
Treated HIV-positive (any ART) versus HIV-negative	PTB	4	2.25 (1.79, 2.81)	0
	sPTB	2	2.14 (1.58, 2.90)	0
	VPTB	1	2.40 (1.23, 4.70)	–
	LBW	2	1.47 (0.93, 2.33)	0
	SGA	3	1.18 (0.76, 1.82)	23

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VPTB, very PTB.

Summary of meta-analysis results for the effect of maternal HIV/ART on perinatal outcomes

Preterm birth (PTB)

The overall meta-analysis of unadjusted effect estimates including 15 cohorts showed that treated HIV-positive women had 1.63 times the risk of having a preterm baby compared with HIV-negative women; however, a high degree of heterogeneity was observed with I^2 value 92.5% (Table 3.2). This finding was consistently observed across cohort design and country-income status. The OR for high-income country (OR = 2.68) was about twice as high as that for LMIC (OR = 1.29) (Table 3.2). Examining the I^2 values of each sub-group, it seemed that much of the heterogeneity was accounted for by cohort design and by country-income status: a high degree of heterogeneity in retrospective (I^2 = 94.5%) and LMIC (I^2 = 89.7%), but no heterogeneity in prospective cohorts (I^2 = 0%) and high-income country (I^2 = 16.4%) respectively (Table 3.2).

Sensitivity analyses according to ART complexity showed that a higher risk of PTB was observed in HIV-positive women receiving HAART than HIV-negative women, and this finding remained irrespective of cohort design and country-income status. However, the finding was not observed when the analysis was restricted to women receiving non HAART (Table 3.2). According to ART class, a higher risk of PTB was observed in HIV-positive women receiving both PI and non PI-based regimens compared with HIV-negative women; those receiving PI (OR = 2.30) had an 80% higher OR than those receiving non PI-based regimens (OR = 1.52) (Table 3.2). According to timing of ART initiation, a higher risk of PTB was observed among HIV-positive women initiating ART pre- but not post-conception, compared with HIV-negative women (Table 3.2).

The meta-analysis of adjusted effect estimates, including four cohorts, showed that the odds of treated HIV-positive women having a preterm baby were 2.25 times as high as the odds of HIV-negative women; no heterogeneity was observed (Table 3.3).

Spontaneous preterm birth (sPTB)

Only three cohorts were available for the meta-analysis of unadjusted effect estimates. These showed that HIV-positive women on ART had more than twice the risk of having a sPTB baby compared with HIV-negative women (Table 3.2). This finding persisted in the meta-analysis of adjusted effect estimates of two cohorts (Table 3.3).

Very preterm birth (VPTB)

The pooled unadjusted effect estimates of four cohorts revealed that HIV-positive women on ART had 2.59 times the risk of having a VPTB baby compared with HIV-negative women; a high degree of heterogeneity was evident (Table 3.2).

Low birth weight (LBW)

The overall meta-analysis of unadjusted effect estimates, including eight cohorts, showed that treated HIV-positive women were 2.30 times more likely to have a LBW baby than HIV-negative women; a high degree of heterogeneity was observed. This finding persisted across country-income status and in the meta-analysis of retrospective, but not prospective cohorts (Table 3.2).

The results of sensitivity analyses restricted to HIV-positive women receiving HAART were similar to the above findings observed in the overall meta-analyses; however, few cohorts (n<5) were included in these sensitivity analyses. Sensitivity analyses restricted to HIV-positive women receiving non HAART were not performed because only one cohort was available (Table 3.2). LBW was significantly more common in treated HIV-positive than HIV-negative women irrespective of ART class: PI and non PI-based regimens, and irrespective of timing of ART initiation: pre-conception or post-conception. HIV-positive women on PI (OR = 3.33) and initiating ART pre-conception (OR = 2.78) showed higher ORs than those on non PI-based regimens (OR = 2.48) and initiating ART post-conception (OR = 2.25) respectively. However, few studies (n<5) were included in these sensitivity analyses (Table 3.2).

Only two cohorts were available for the meta-analysis of adjusted effect estimates, which showed no difference in LBW risk between treated HIV-positive and HIV-negative pregnant women (Table 3.3).

Very low birth weight (VLBW)

The pooled unadjusted effect estimates of three cohorts in which all HIV-positive women received HAART, showed no difference in VLBW risk between treated HIV-positive and HIV-negative pregnant women (Table 3.2). Very few data were available for the sensitivity analyses according to ART class, and timing of treatment initiation: HIV-positive women receiving PI-based regimens (but not non-PI), and initiating ART post-conception (but not pre-conception) showed a higher risk of VLBW compared with HIV-negative women (Table 3.2).

Small for gestational age (SGA)

The synthesis of unadjusted effect estimates, including nine cohorts, revealed that SGA was significantly more common in treated HIV-positive than HIV-negative women with OR = 2.45 (Table 3.2). Sub-group analyses by cohort design showed similar findings for the six retrospective, but not the three prospective cohorts. Similar findings were also observed in the meta-analysis of five cohorts of high-income country with an OR more than double that obtained in the overall analysis (OR = 5.68); however, the meta-analysis of four LMIC cohorts did not report the same finding (Table 3.2). In sensitivity analyses according to ART complexity and class/timing of ART initiation, only HIV-positive women on HAART showed a higher risk of SGA compared with HIV-negative women (Table 3.2). However,

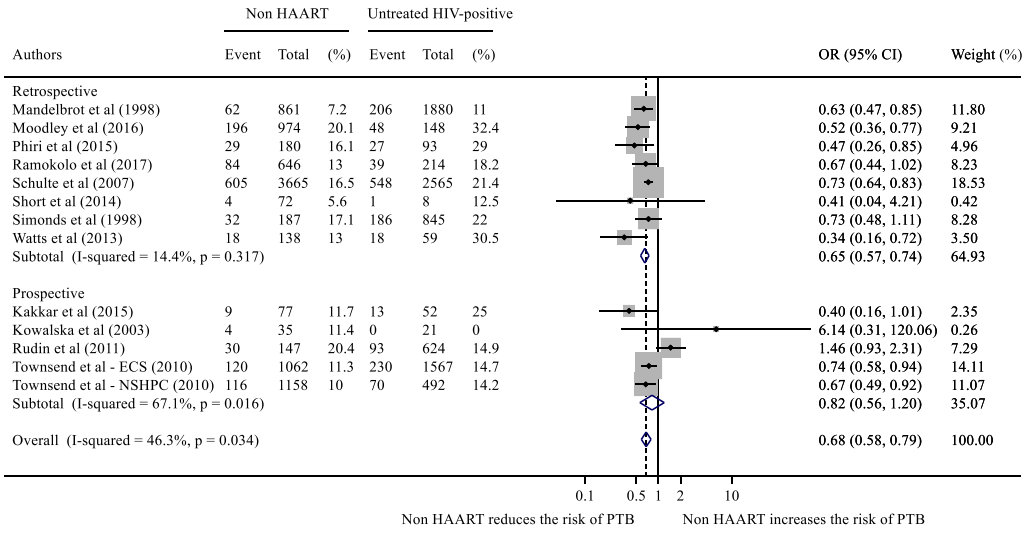
the I^2 values suggested a high degree of heterogeneity in the overall sub-group and sensitivity analyses (Table 3.2).

Only three cohorts were available for the synthesis of adjusted effect estimates, which showed no association between maternal HIV/ART and SGA compared with HIV-negative women; no heterogeneity was observed (Table 3.3).

Appendix 3.8
Sensitivity analyses and summary of meta-analysis results: effect of maternal ART on adverse perinatal outcomes.

Preterm birth

A



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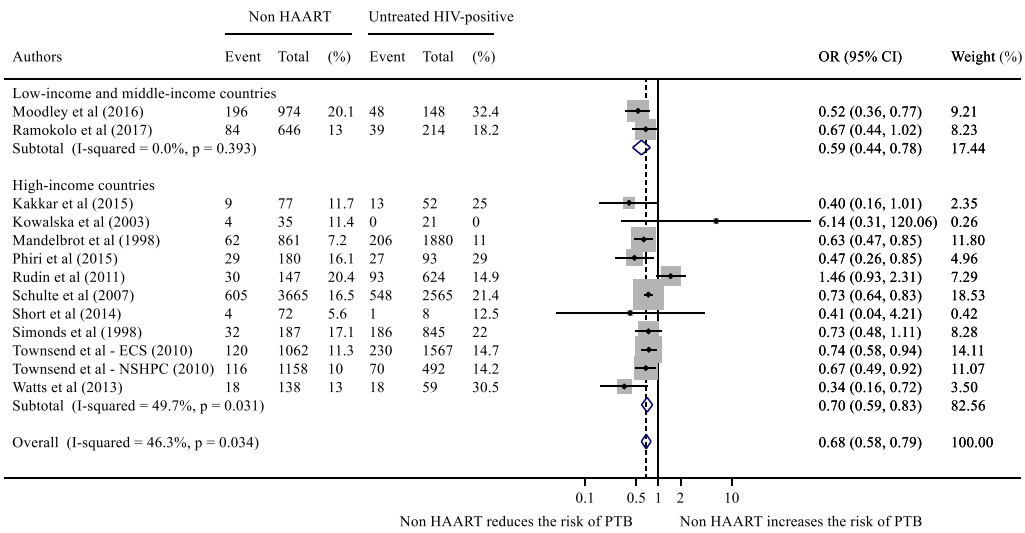


Figure 3.15. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non HAART versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

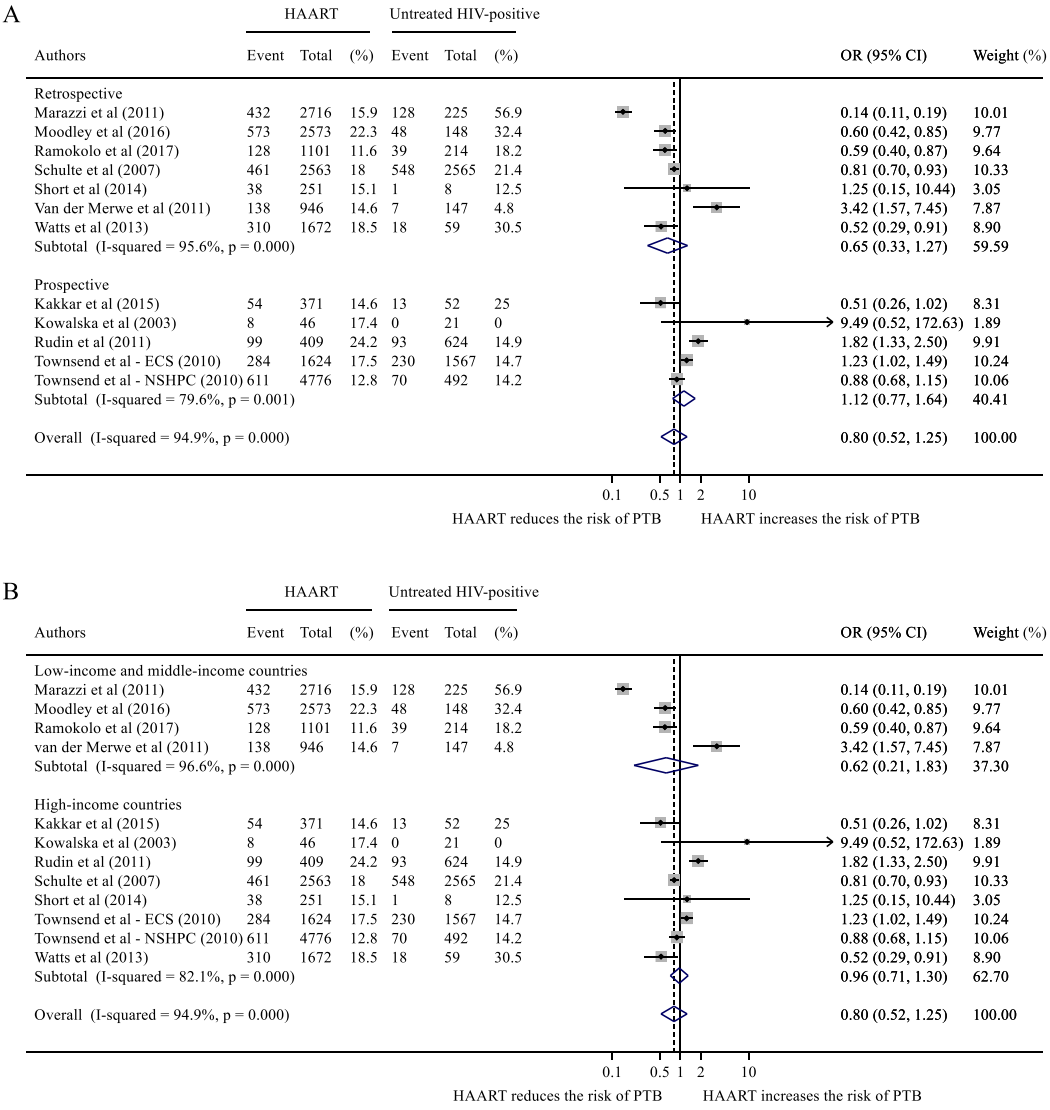


Figure 3.16. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

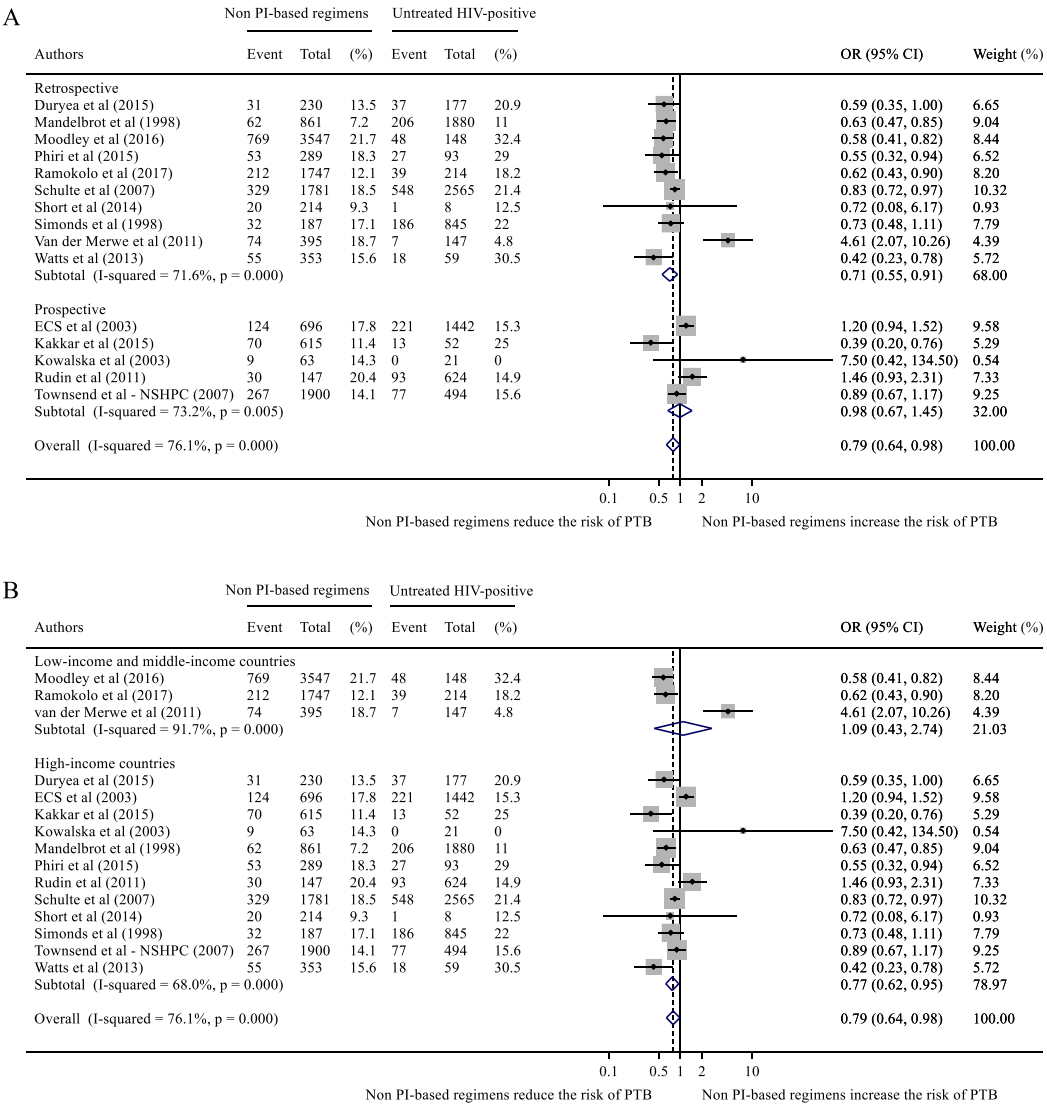


Figure 3.17. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non PI-based regimens versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

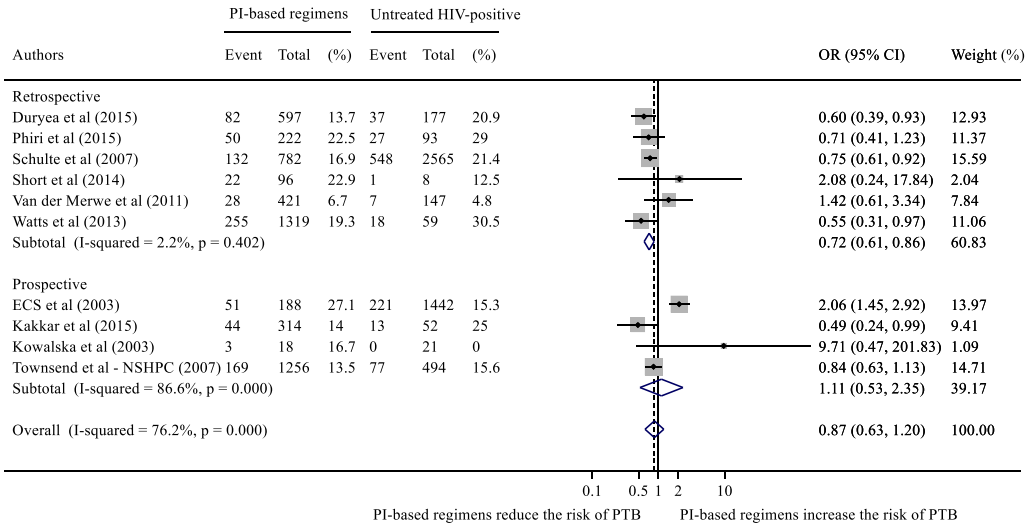


Figure 3.18. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with PI-based regimens versus untreated HIV-positive pregnant women using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

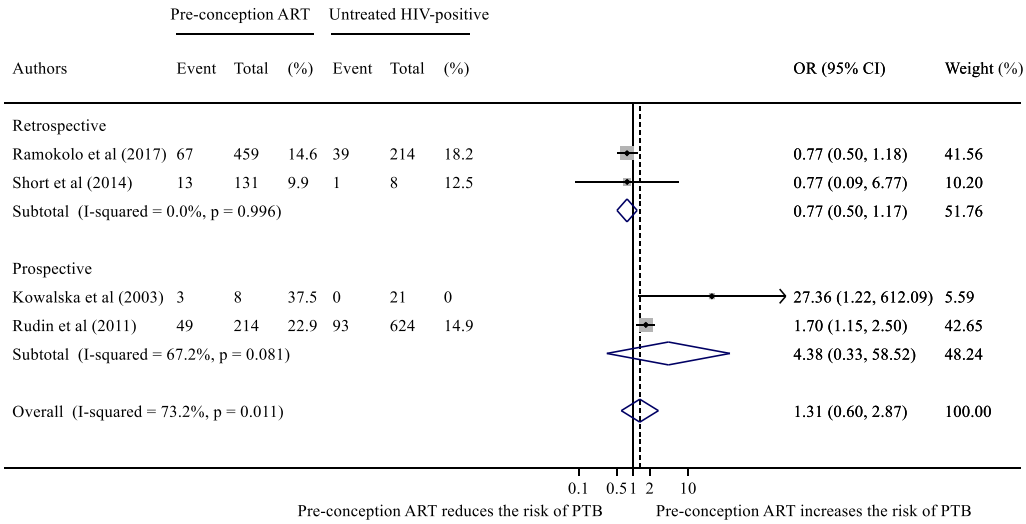


Figure 3.19. Forest plot of risk of preterm birth in treated HIV-positive pregnant women who initiated ART pre-conception versus untreated HIV-positive pregnant women using unadjusted data, by cohort design. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

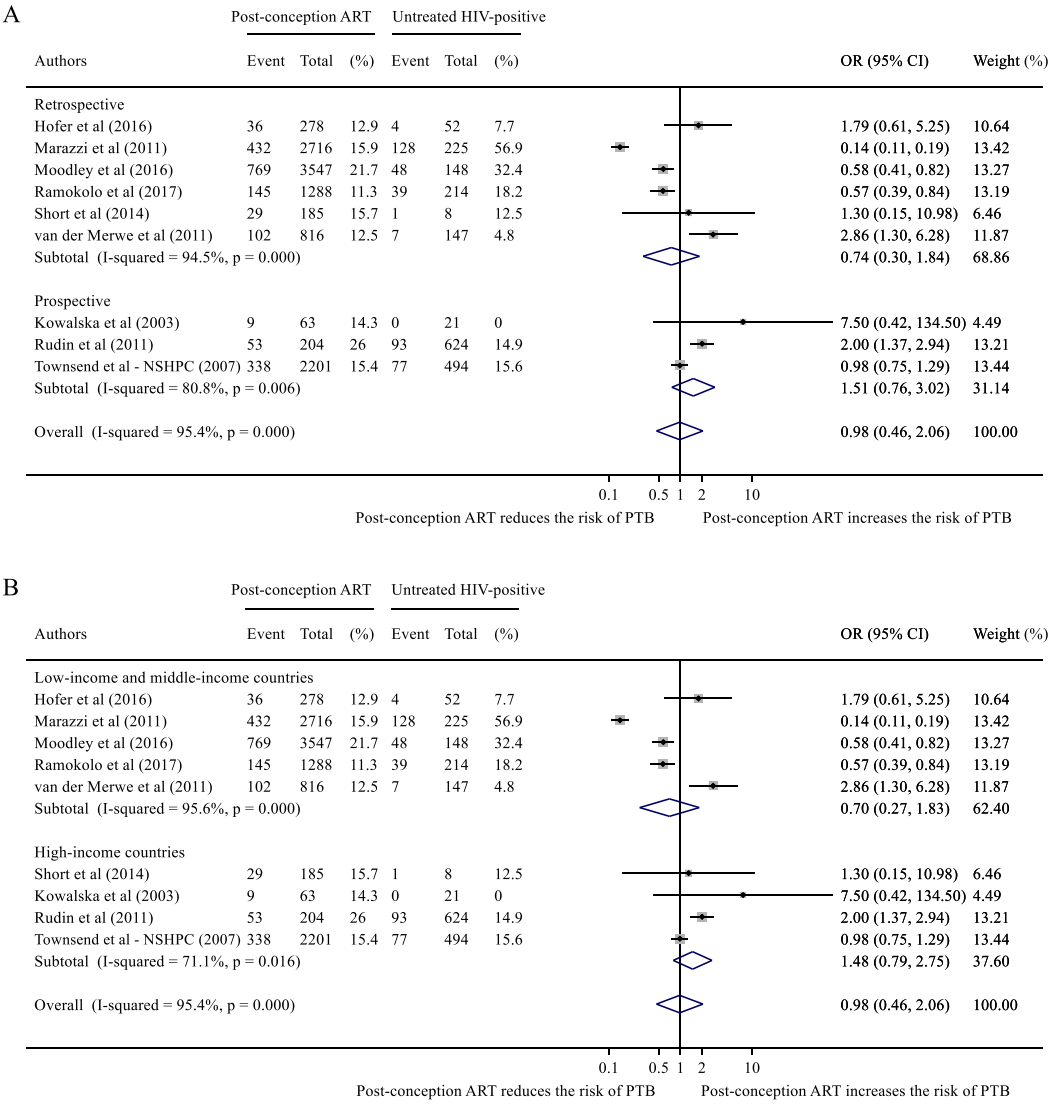


Figure 3.20. Forest plots of risk of preterm birth in treated HIV-positive pregnant women who initiated ART post-conception versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Low birth weight

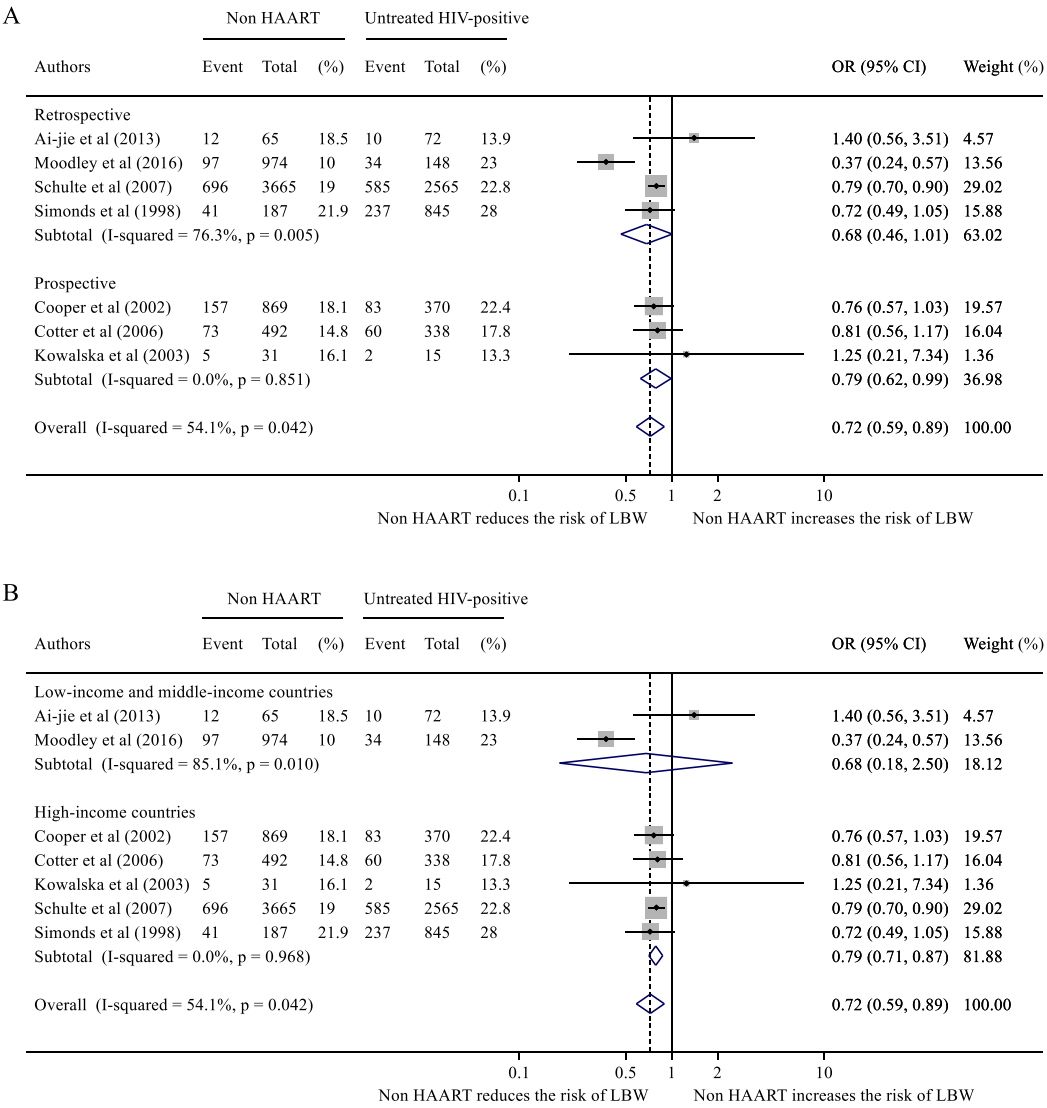


Figure 3.21. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non HAART versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

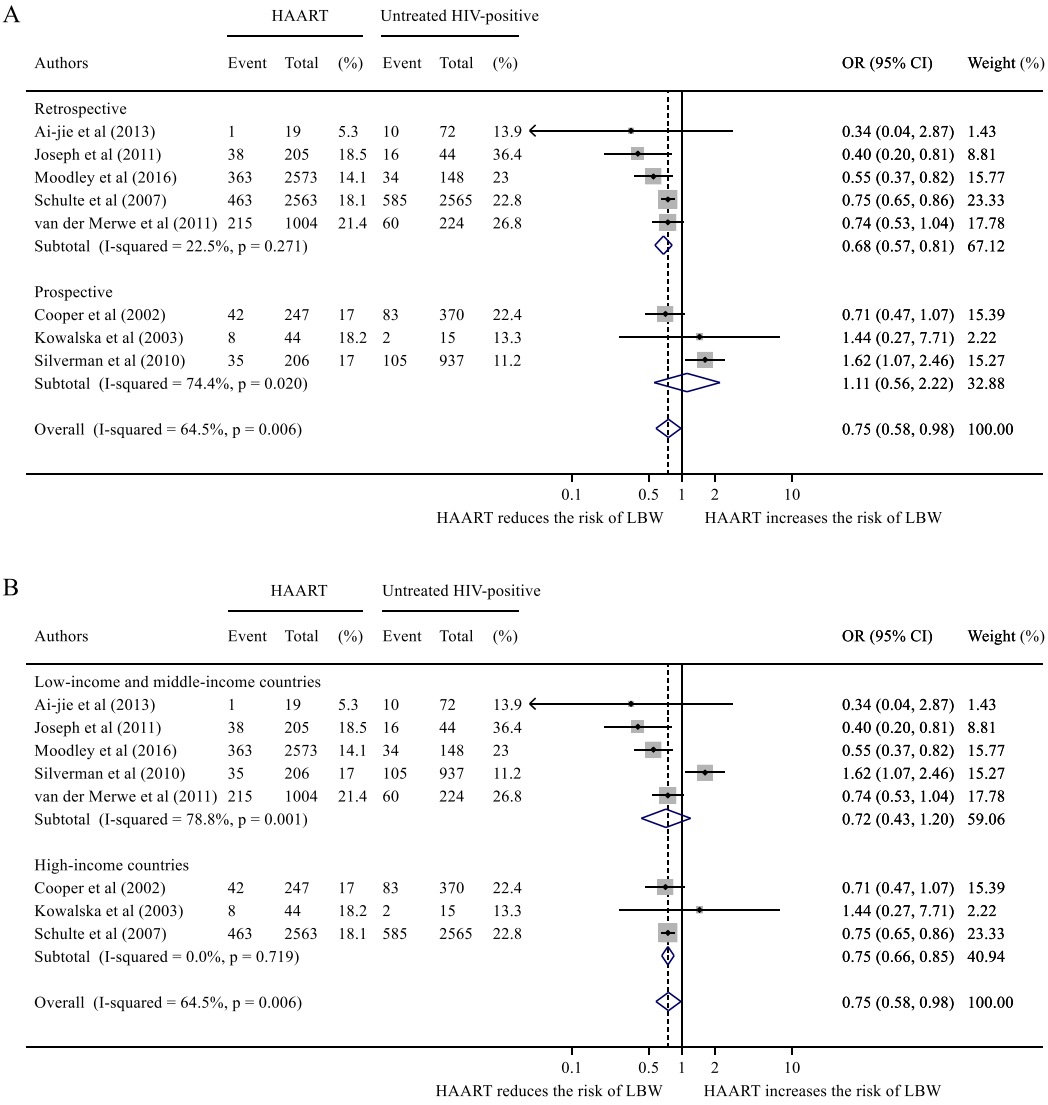


Figure 3.22. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with HAART versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

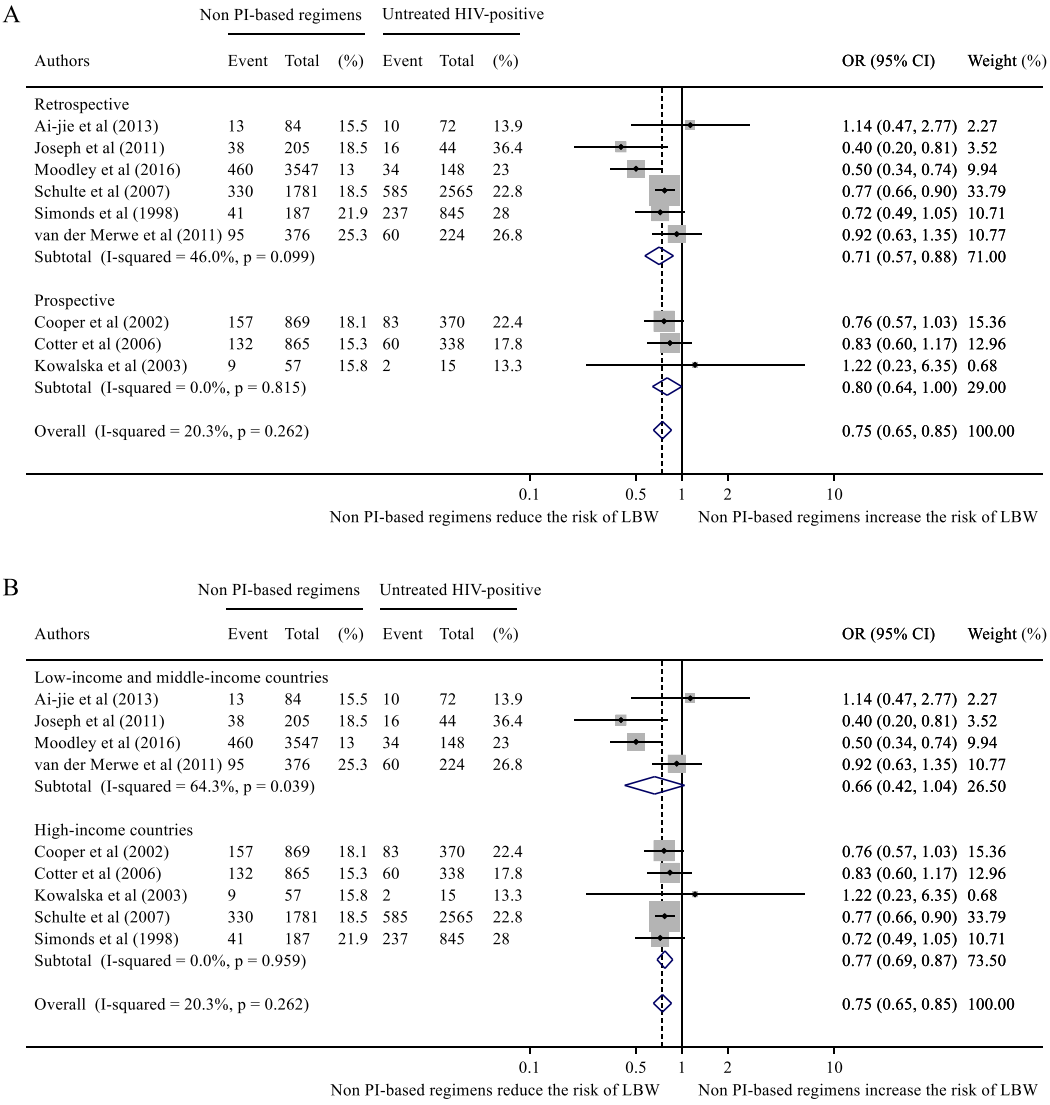


Figure 3.23. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non PI-based regimens versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

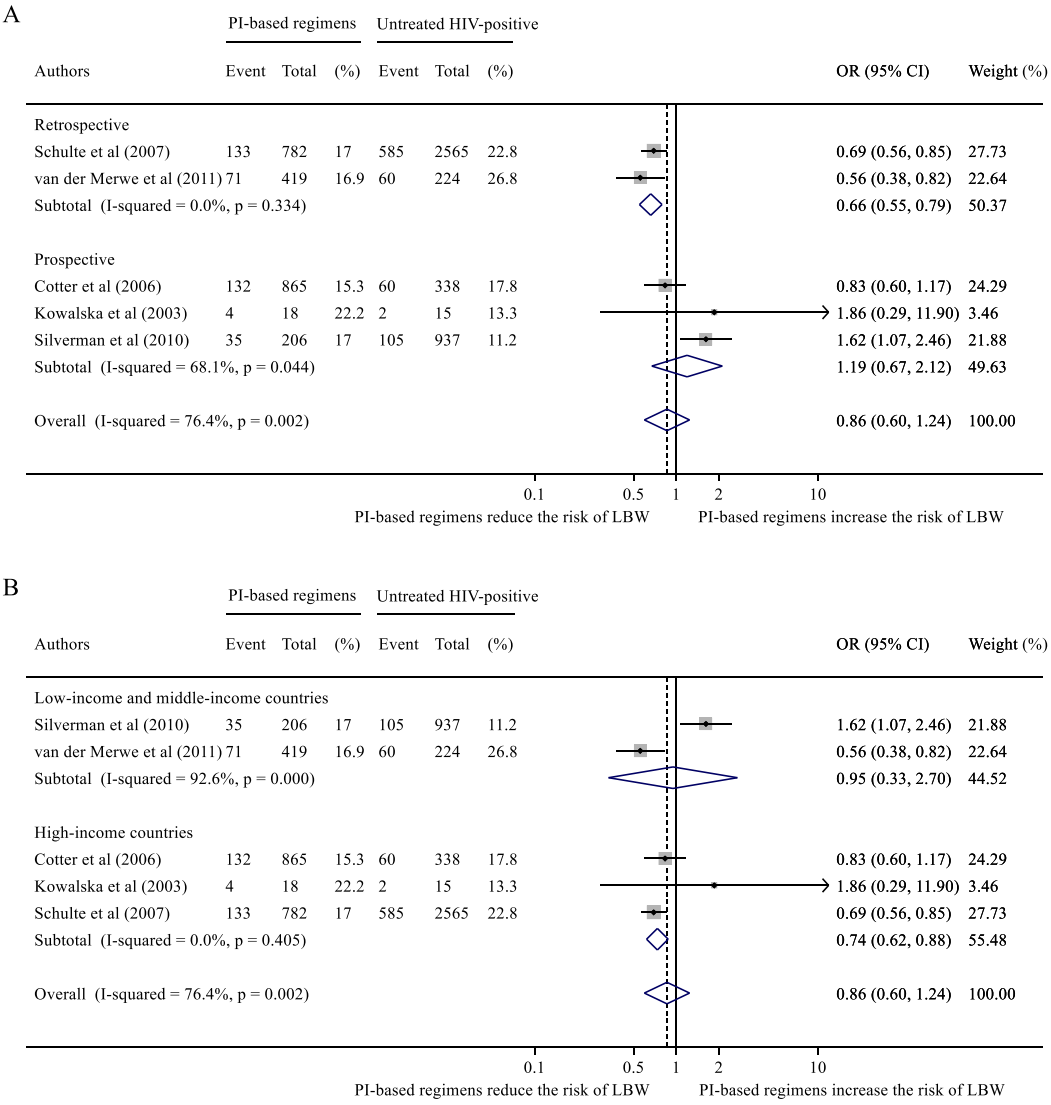
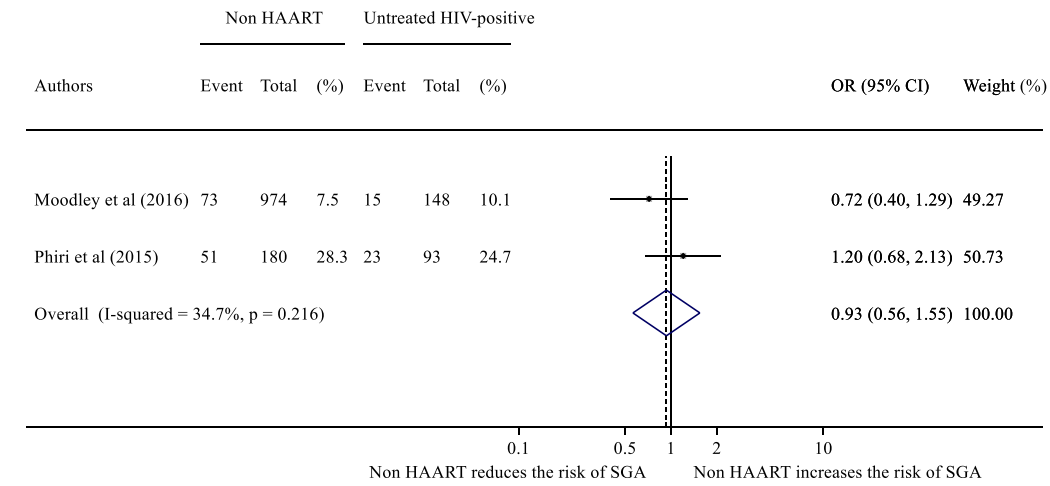


Figure 3.24. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with PI-based regimens versus untreated HIV-positive pregnant women using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

Small for gestational age

A



B

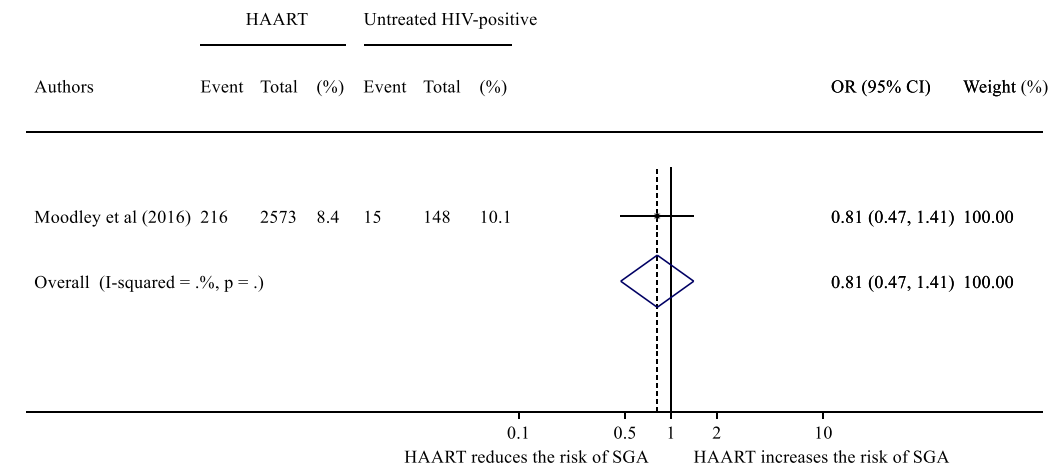
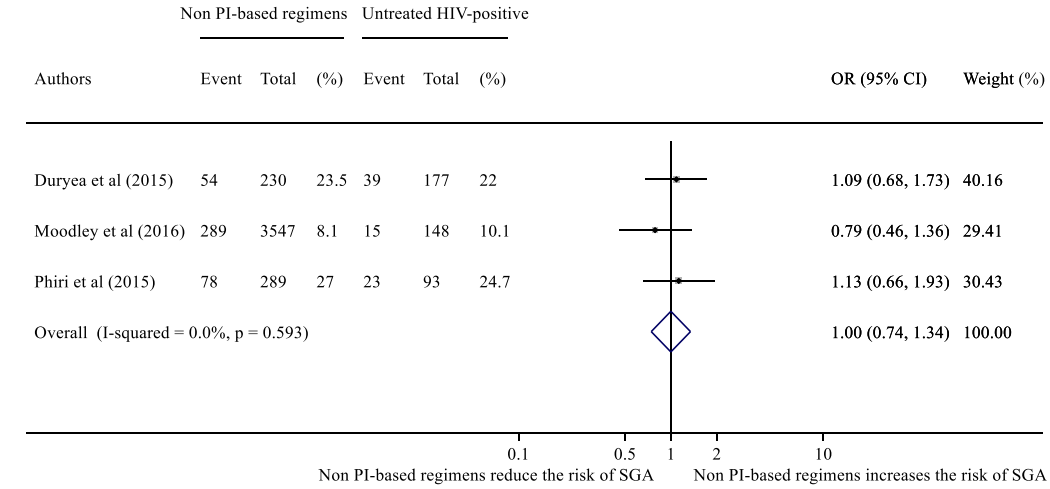


Figure 3.25. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with non HAART (A) or HAART (B) versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

A



B

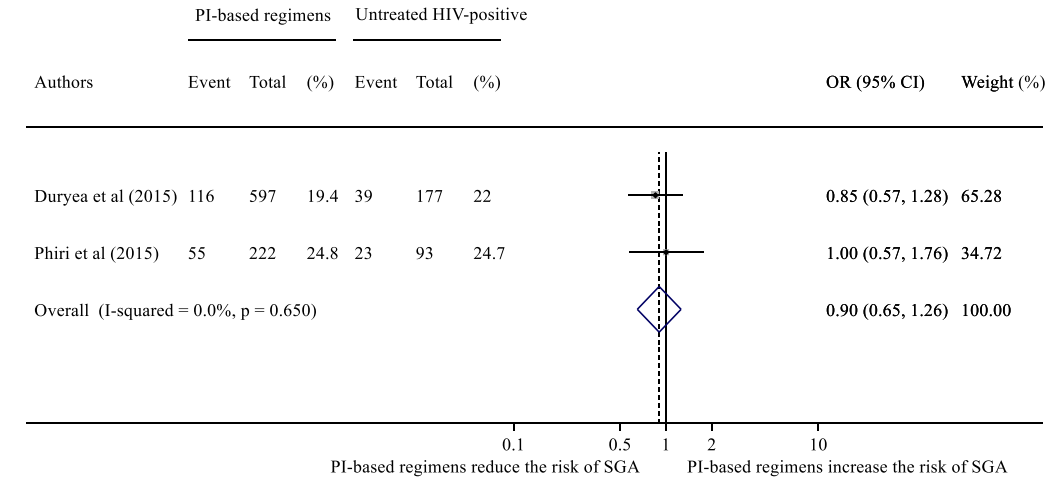


Figure 3.26. Forest plots of risk of small for gestational age in HIV-positive pregnant women treated with non PI (A) or PI-based regimens (B) versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; SGA, small for gestational age.

Very small for gestational age

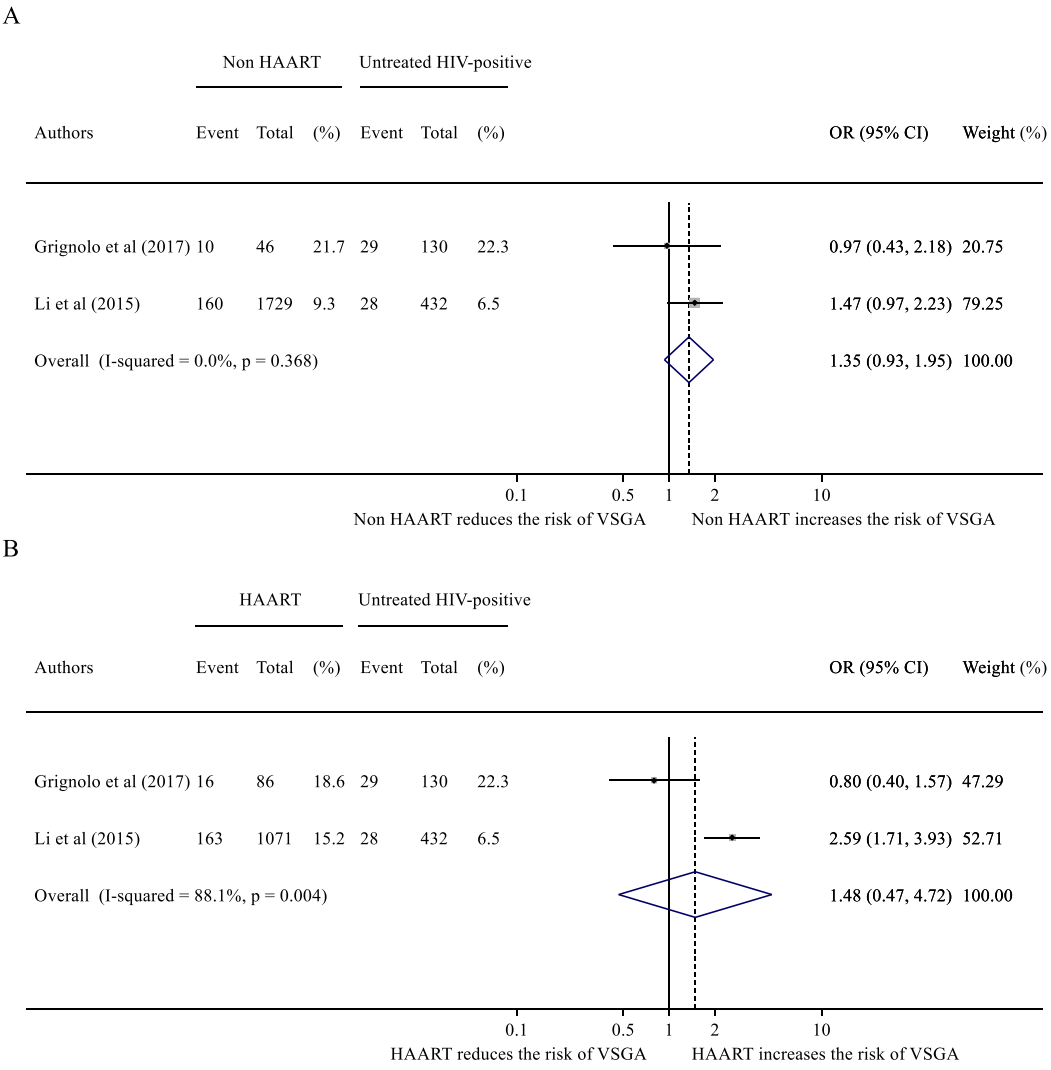
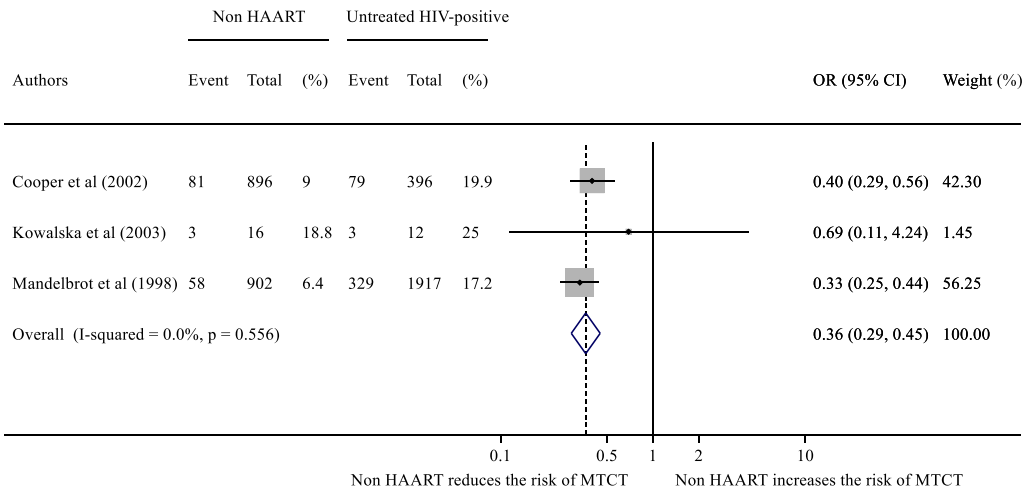


Figure 3.27. Forest plots of risk of very small for gestational age in HIV-positive pregnant women treated with non HAART (A) or HAART (B) versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

Mother-to-child transmission

A



B

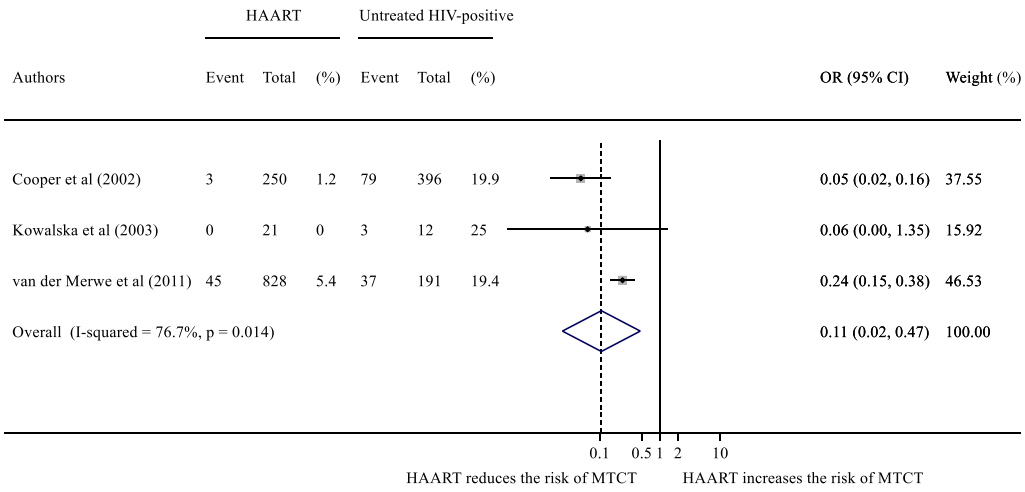


Figure 3.28. Forest plots of risk of mother-to-child transmission in HIV-positive pregnant women treated with non HAART (A) or HAART (B) versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio.

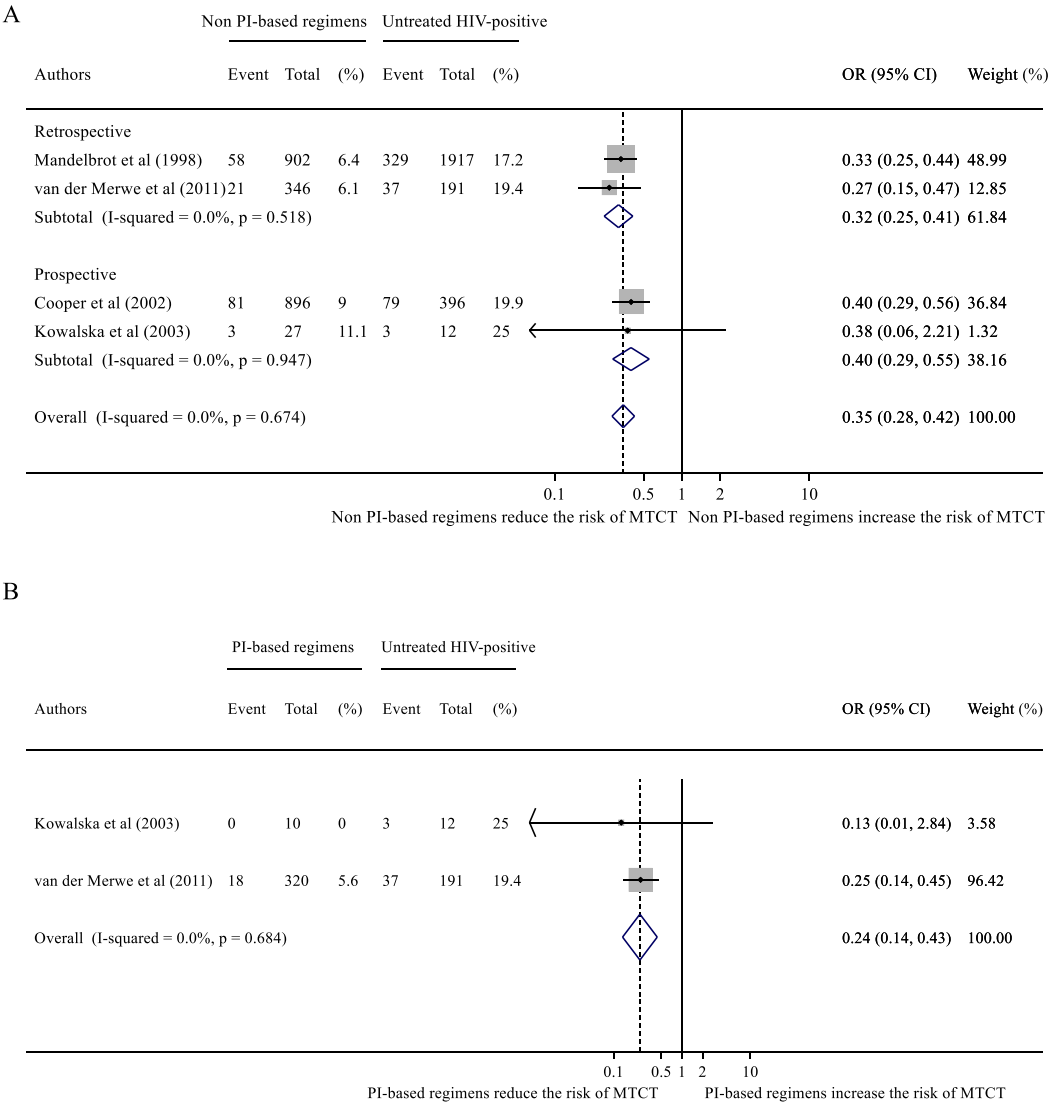


Figure 3.29. Forest plots of risk of mother-to-child transmission in HIV-positive pregnant women treated with non PI (A) and PI-based regimens (B) versus untreated HIV-positive pregnant women using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; OR, odds ratio; PI, protease inhibitor.

Table 3.4. Summary of meta-analysis results for the effect of maternal ART on perinatal outcomes using unadjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Treated HIV-positive (any ART) versus untreated HIV-positive	PTB	17	0.74 (0.55, 1.00)	92.2	12	0.66 (0.45, 0.97)	92.1	5	1.00 (0.68, 1.48)	82.1	5	0.75 (0.28, 2.01)	96	12	0.79 (0.64, 0.97)	77.2
	sPTB	1	0.39 (0.20, 0.73)	–												
	VPTB	1	1.89 (0.82, 4.36)	–												
	LBW	11	0.80 (0.68, 0.94)	58.1	6	0.69 (0.58, 0.84)	39.5	5	0.96 (0.75, 1.23)	57.7	5	0.77 (0.47, 1.27)	80.9	6	0.80 (0.73, 0.87)	0
	VLBW	2	0.49 (0.29, 0.83)	15.3												
	SGA	3	0.92 (0.70, 1.21)	0												
	VSGA	2	1.31 (0.60, 2.84)	78.7												
	MTCT	4	0.31 (0.25, 0.37)	0	2	0.30 (0.22, 0.40)	28.4	2	0.32 (0.23, 0.44)	0						
Non HAART versus untreated HIV-positive	PTB	13	0.68 (0.58, 0.79)	46.3	8	0.65 (0.57, 0.74)	14.4	5	0.82 (0.56, 1.20)	67.1	2	0.59 (0.44, 0.78)	0	11	0.70 (0.59, 0.83)	49.7
	LBW	7	0.72 (0.59, 0.89)	54.1	4	0.68 (0.46, 1.01)	76.3	3	0.79 (0.62, 0.99)	0	2	0.68 (0.18, 2.50)	85.1	5	0.79 (0.71, 0.87)	0
	SGA	2	0.93 (0.56, 1.55)	34.7												
	VSGA	2	1.35 (0.93, 1.95)	0												
	MTCT	3	0.36 (0.29, 0.45)	0												
HAART versus untreated HIV-positive	PTB	12	0.80 (0.52, 1.25)	94.9	7	0.65 (0.33, 1.27)	95.6	5	1.12 (0.77, 1.64)	79.6	4	0.62 (0.21, 1.83)	96.6	8	0.96 (0.71, 1.30)	82.1
	LBW	8	0.75 (0.58, 0.98)	64.5	5	0.68 (0.57, 0.81)	22.5	3	1.11 (0.56, 2.22)	74.4	5	0.72 (0.43, 1.20)	78.8	3	0.75 (0.66, 0.85)	0
	SGA	1	0.81 (0.47, 1.41)	–												
	VSGA	2	1.48 (0.47, 4.72)	88.1												
	MTCT	3	0.11 (0.02, 0.47)	76.7												

Table 3.4. Summary of meta-analysis results for the effect of maternal ART on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Non PI-based regimens versus untreated HIV-positive	PTB	15	0.79 (0.64, 0.98)	76.1	10	0.71 (0.55, 0.91)	71.6	5	0.98 (0.67, 1.45)	73.2	3	1.09 (0.43, 2.74)	91.7	12	0.77 (0.62, 0.95)	68
	LBW	9	0.75 (0.65, 0.85)	20.3	6	0.71 (0.57, 0.88)	46	3	0.80 (0.64, 1.00)	0	4	0.66 (0.42, 1.04)	64.3	5	0.77 (0.69, 0.87)	0
	SGA	3	1.00 (0.74, 1.34)	0												
	MTCT	4	0.35 (0.28, 0.42)	0	2	0.32 (0.25, 0.41)	0	2	0.40 (0.29, 0.55)	0						
PI-based regimens versus untreated HIV-positive	PTB	10	0.87 (0.63, 1.20)	76.2	6	0.72 (0.61, 0.86)	2.2	4	1.11 (0.53, 2.35)	86.6						
	LBW	5	0.86 (0.60, 1.24)	76.4	2	0.66 (0.55, 0.79)	0	3	1.19 (0.67, 2.12)	68.1	2	0.95 (0.33, 2.70)	92.6	3	0.74 (0.62, 0.88)	0
	SGA	2	0.90 (0.65, 1.26)	0												
	MTCT	2	0.24 (0.14, 0.43)	0												
Pre-conception ART versus untreated HIV-positive	PTB	4	1.31 (0.60, 2.87)	73.2	2	0.77 (0.50, 1.17)	0	2	4.38 (0.33, 58.52)	67.2						
Post-conception ART versus untreated HIV-positive	PTB	9	0.98 (0.46, 2.06)	95.4	6	0.74 (0.30, 1.84)	94.5	3	1.51 (0.76, 3.02)	80.8	5	0.70 (0.27, 1.83)	95.6	4	1.48 (0.79, 2.75)	71.1

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; MTCT, mother-to-child transmission; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Table 3.5. Summary of meta-analysis results for the effect of maternal ART on perinatal outcomes using adjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis		
		N	OR (95% CI)	I^2 (%)
Treated HIV-positive (any ART) versus untreated HIV-positive	PTB	5	0.84 (0.74, 0.94)	0
	SGA	3	1.09 (0.80, 1.48)	0
Monotherapy versus untreated HIV-positive	SGA	2	0.76 (0.25, 2.31)	54.6
Non HAART versus untreated HIV-positive	PTB	3	0.62 (0.33, 1.18)	78.7
HAART versus untreated HIV-positive	PTB	3	1.18 (0.25, 5.70)	93
Efavirenz-based HAART versus untreated HIV-positive	PTB	2	1.33 (0.08, 22.82)	93.5
	LBW	2	0.36 (0.04, 2.95)	89.4
	SGA	1	0.25 (0.07, 0.87)	–
Nevirapine-based HAART versus untreated HIV-positive	PTB	3	0.84 (0.16, 4.33)	92.2
	LBW	3	0.34 (0.10, 1.17)	89.8
	SGA	2	0.72 (0.15, 3.40)	80.2
PI-based HAART versus untreated HIV-positive	PTB	3	2.52 (1.03, 6.13)	59.9
	LBW	1	0.45 (0.19, 1.06)	–

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age.

Summary of meta-analysis results for the effect of maternal ART on perinatal outcomes

Preterm birth (PTB)

The overall meta-analysis of unadjusted effect estimates including 17 cohorts showed a 26% reduction in the odds of having a preterm baby in HIV-positive women treated with any ART compared with those untreated (Table 3.4). Sub-group analyses by cohort design showed a 34% reduction in retrospective, but not prospective cohorts (Table 3.4). Sub-group analyses by country-income status showed a 21% reduction in cohorts of high-income countries, but not LMICs

(Table 3.4). However, the I^2 values indicated a high degree of heterogeneity in the overall meta-analysis and even in each sub-group analysis (Table 3.4).

In sensitivity analyses according to ART complexity, HIV-positive women receiving non HAART showed a 32% reduction in the odds of having a preterm baby compared with those receiving no ART; however the finding was not observed in HIV-positive women receiving HAART (Table 3.4). Regarding ART class, the odds of having a preterm baby in HIV-positive women receiving non PI-based regimens were reduced by approximately 20% compared with women receiving no ART; however, the finding was not observed in HIV-positive women receiving PI-based regimens (Table 3.4). There was insufficient evidence to show a difference in the odds of having a preterm baby in HIV-positive women initiating ART pre-conception and post-conception versus women receiving no ART (Table 3.4).

The pooled adjusted effect estimates, including five cohorts, showed that taking ART during pregnancy was associated with a 16% reduction in the odds of having a preterm baby compared with not taking ART; no heterogeneity was evident. However, for women treated with PI-based HAART, the odds of having a preterm baby were 2.52 times as large as the odds for those untreated (Table 3.5).

Low birth weight (LBW)

The pooled unadjusted effect estimates of 11 cohorts showed an association between being treated during pregnancy and a 20% reduction in the odds of having a LBW baby compared with being untreated; moderate heterogeneity was evident (Table 3.4). In sub-group analyses by cohort design, the association

remained in retrospective cohort with a reduction of approximately 30%, but not in prospective cohorts (Table 3.4). In sub-group analyses by country-income status, the association remained in cohorts conducted in high-income country with a reduction of 20%, but not in LMIC (Table 3.4). The I^2 values suggested that much of the heterogeneity in the overall analysis was accounted for by country income status: a high degree of heterogeneity in LMIC (I^2 = 80.9%), but no heterogeneity in high-income country (I^2 = 0%) (Table 3.4).

Sensitivity analyses showed that the association between ART and a reduced risk of LBW remained irrespective of ART complexity, with 28% and 25% reductions in the odds of having a LBW baby for non HAART and HAART, respectively (Table 3.4). According to ART class, only PI-based regimens, that have reduced the odds of having a LBW baby by 25%, compared with no ART (Table 3.4).

Very low birth weight (VLBW)

For HIV-positive women on ART, the odds of having a VLBW baby were reduced by approximately 50% compared with women not on ART; however, only two cohorts were included in this unadjusted meta-analysis (Table 3.4).

Small for gestational age (SGA)

Only three cohorts were available for the meta-analysis of unadjusted effect estimates, suggesting that there was insufficient evidence to show a difference in SGA risk between treated and untreated HIV-positive women (Table 3.4). This finding remained irrespective of ART complexity and class (Table 3.4), and in the meta-analyses of adjusted effect estimates (Table 3.5).

Very small for gestational age (VSGA)

The meta-analysis of unadjusted effect estimates, including two cohorts, was unable to show sufficient evidence for the association between ART and VSGA (Table 3.4).

Mother-to-child transmission (MTCT)

The pooled unadjusted effect estimates, including four cohorts, showed that taking ART during pregnancy reduced the odds of MTCT by approximately 70% compared with not taking ART (Table 3.4). This finding was consistently observed across cohort design (retrospective and prospective), and ART complexity (non HAART and HAART) and class (non PI and PI-based regimens) (Table 3.4).

Appendix 3.9
Sensitivity analyses and summary of meta-analysis results: effect of ART complexity on adverse perinatal outcomes.

Preterm birth

Combination therapy versus monotherapy

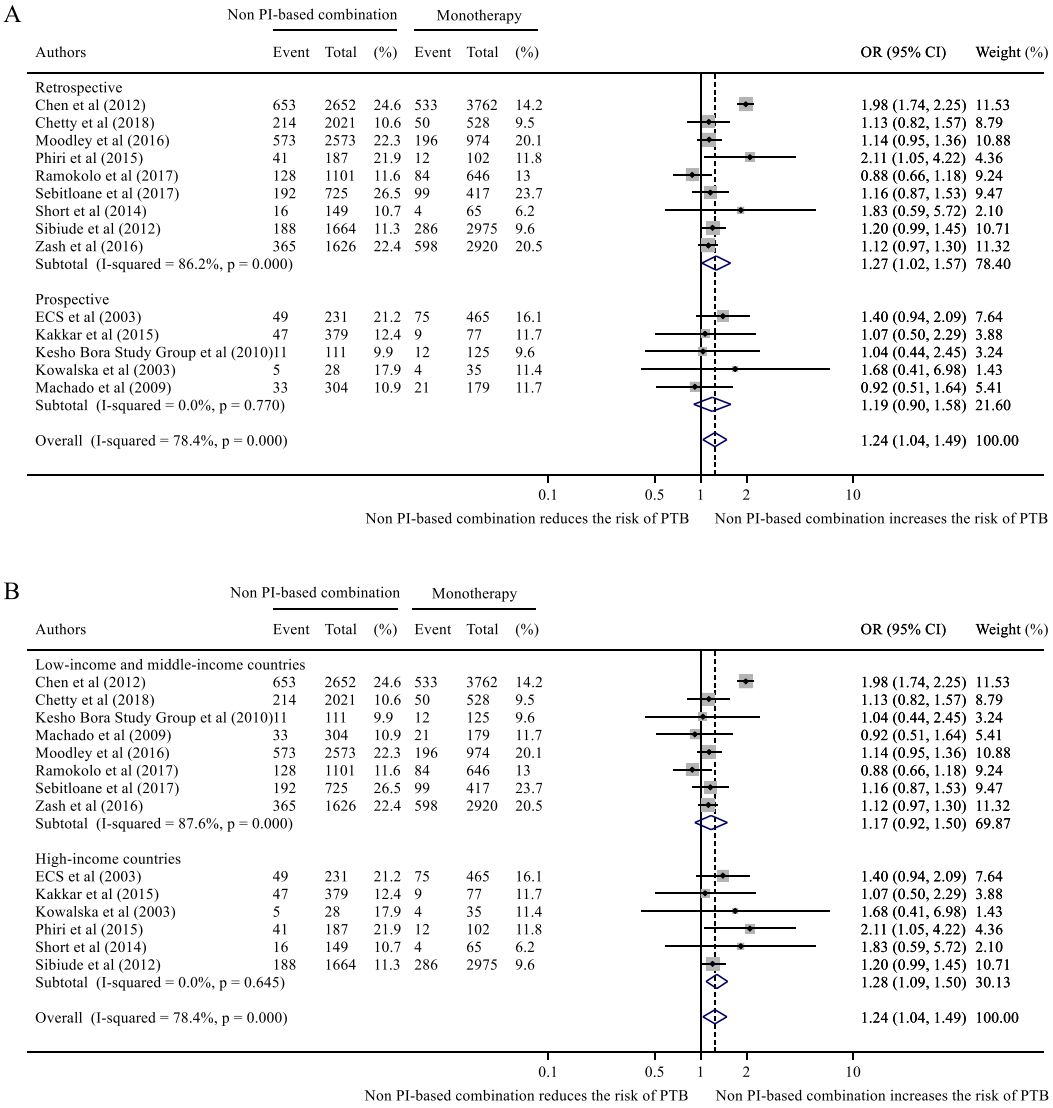


Figure 3.30. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non PI-based combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth

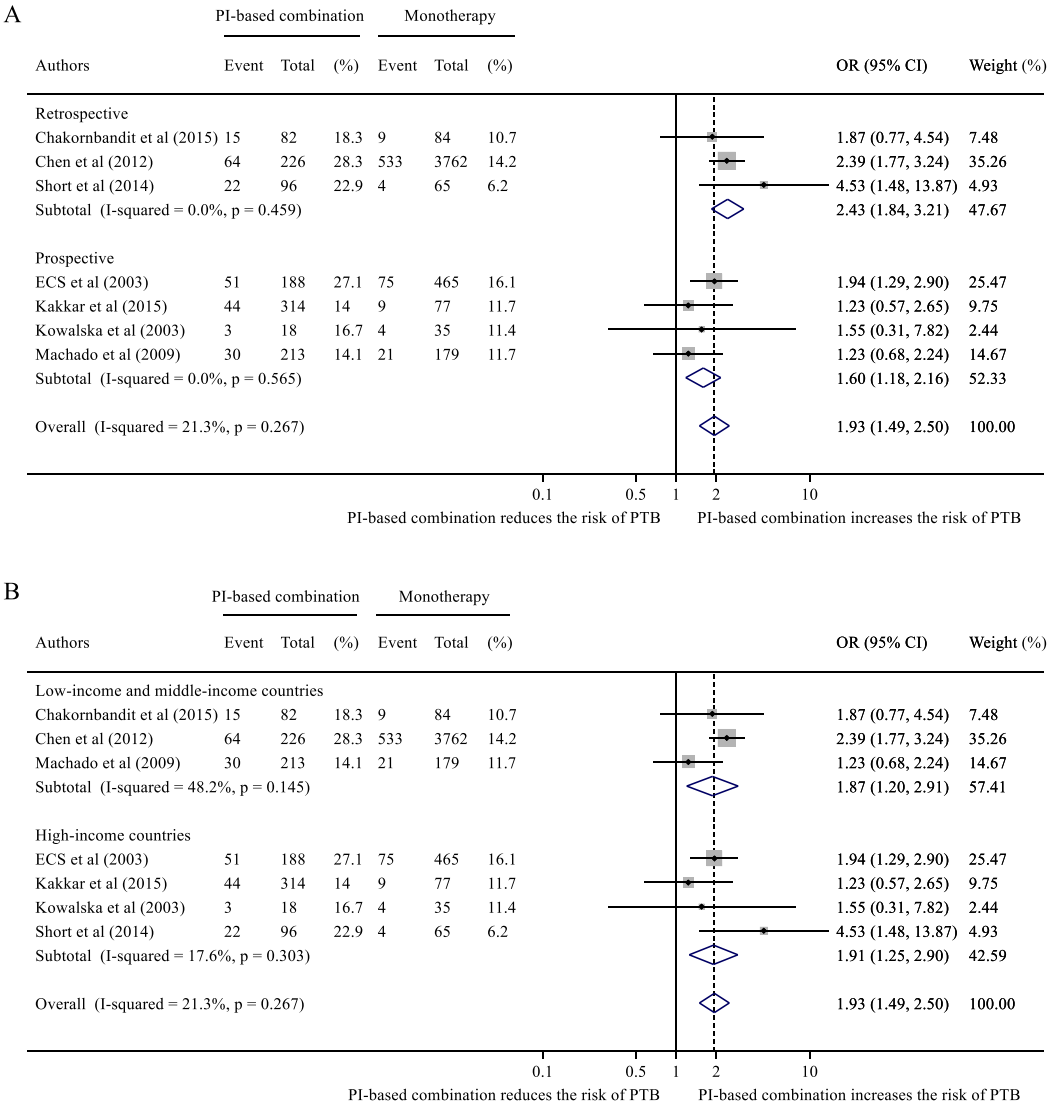


Figure 3.31. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI-based combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

HAART versus monotherapy

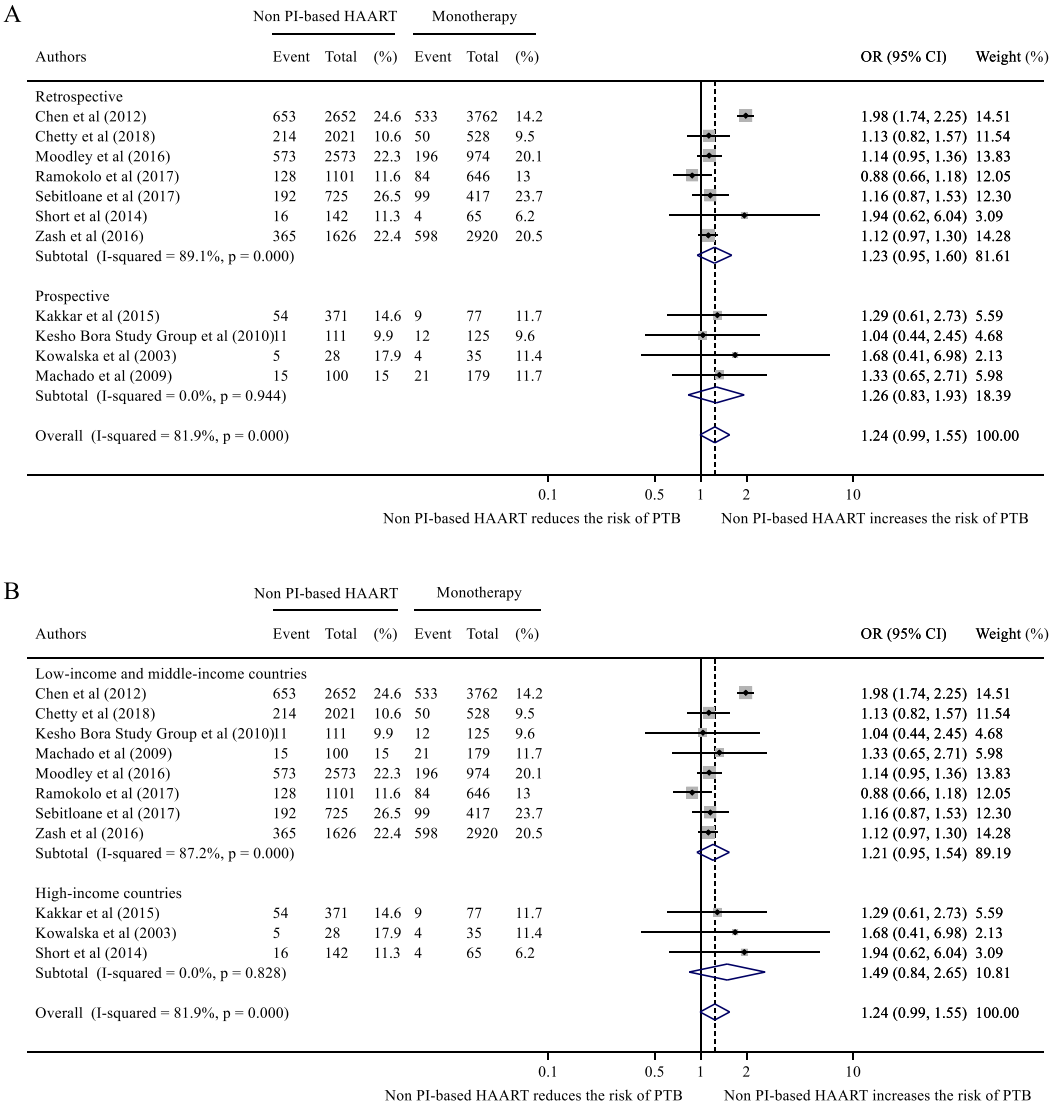


Figure 3.32. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non PI-based HAART versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

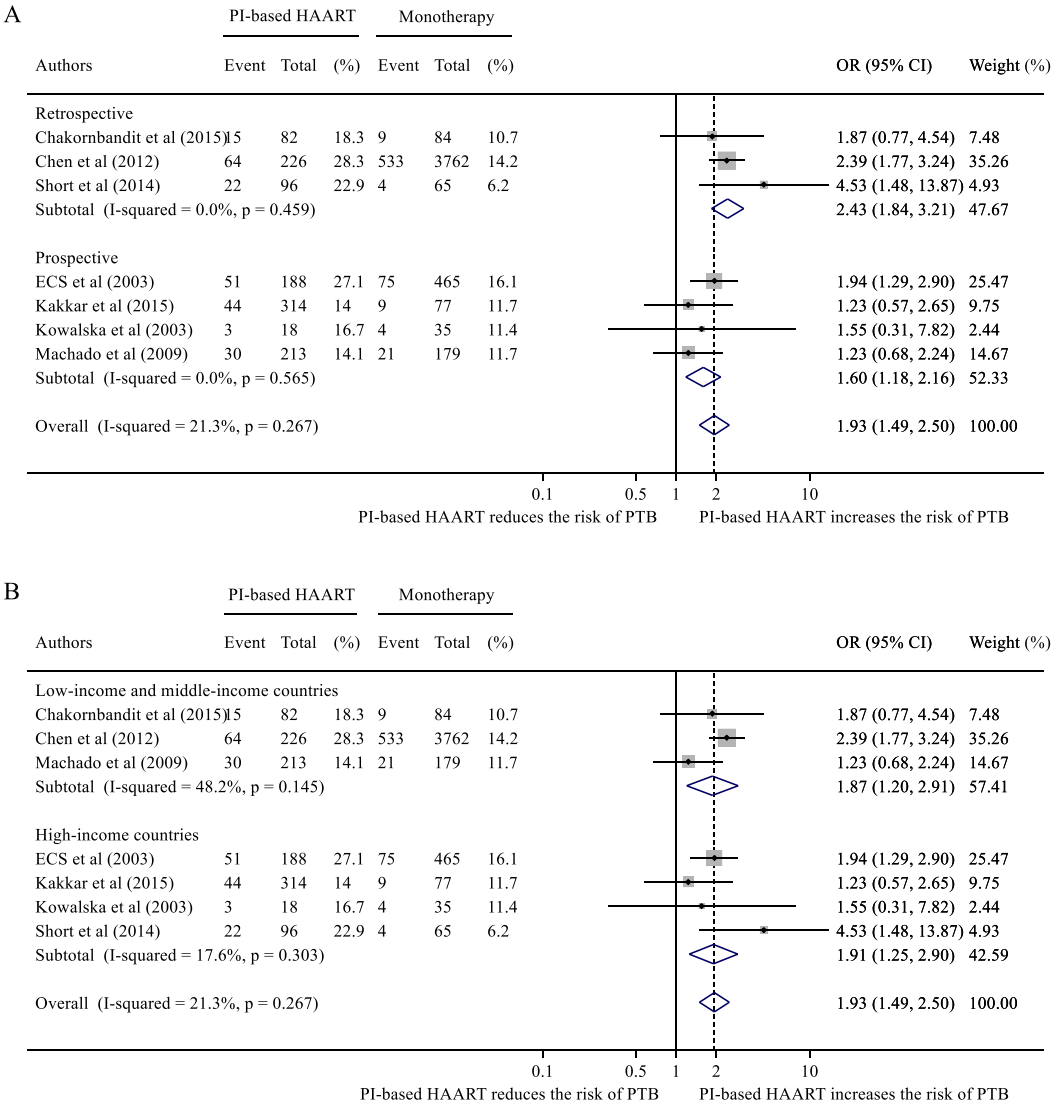


Figure 3.33. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI-based HAART versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

HAART versus non HAART

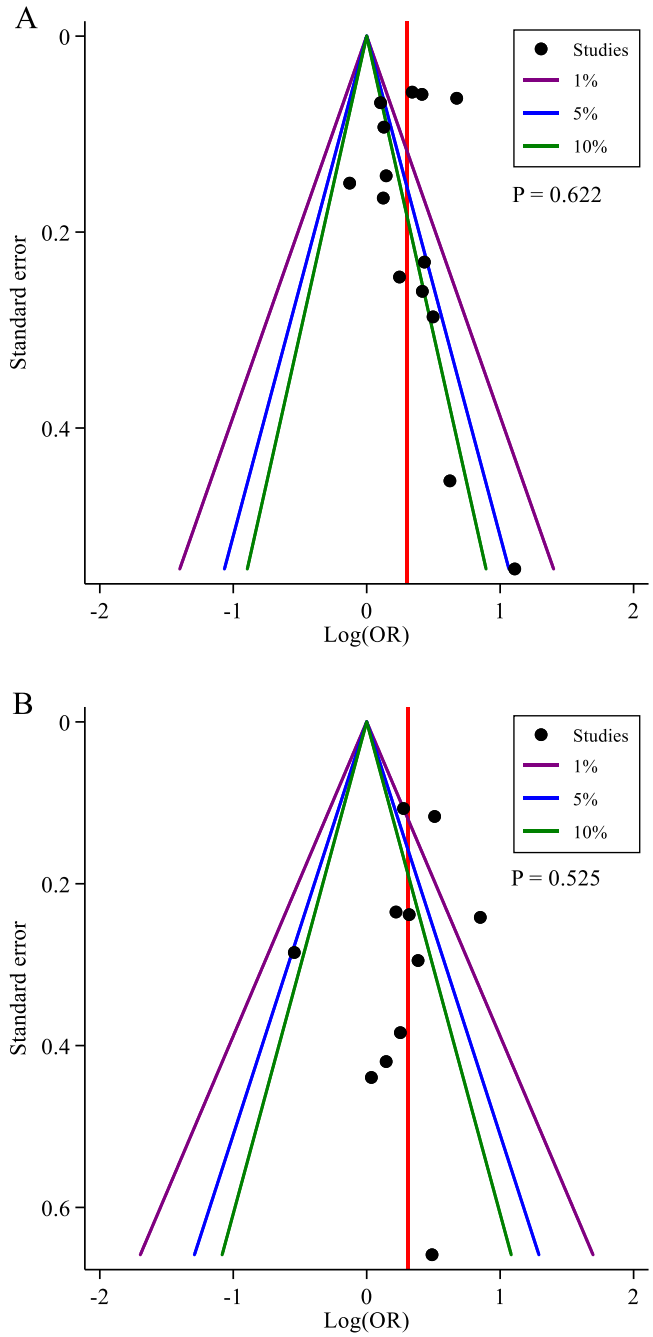


Figure 3.34. Contour-enhanced funnel plots of the cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data, by cohort design: retrospective, n=14 (A) and prospective, n=11 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio.

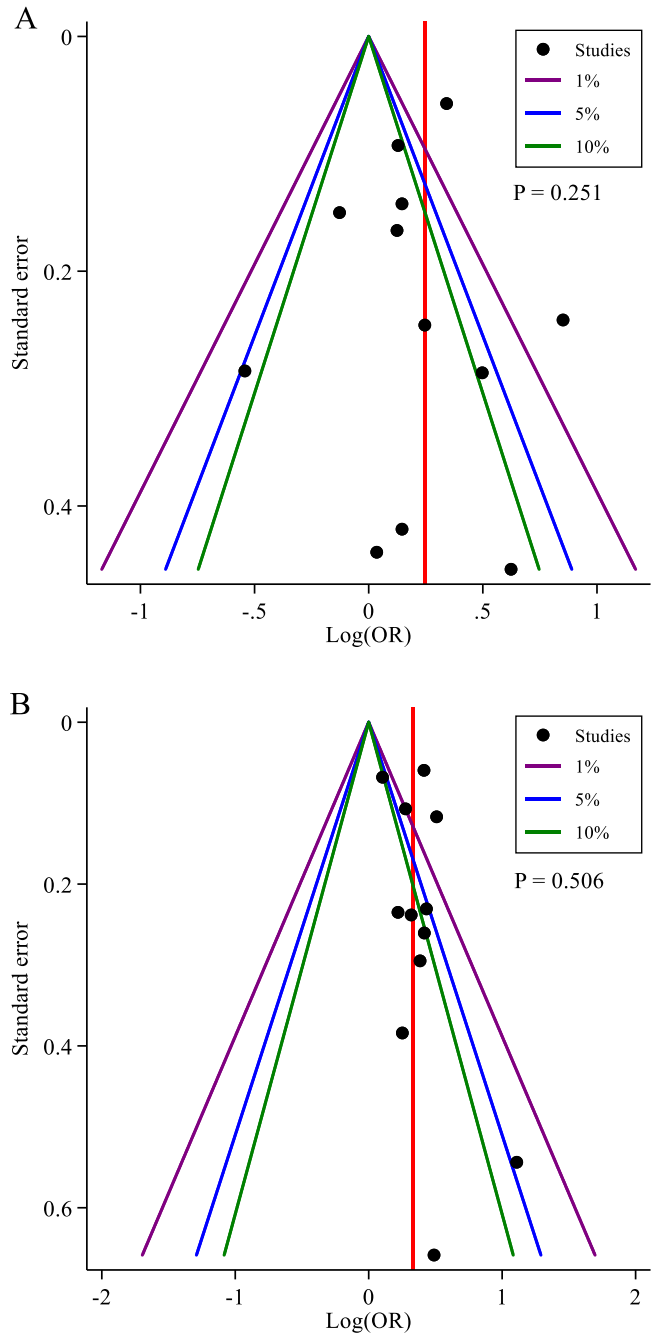


Figure 3.35. Contour-enhanced funnel plots of the cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART using unadjusted data, by country-income status: low and middle-income, n=13 (A) and high-income, n=12 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio.

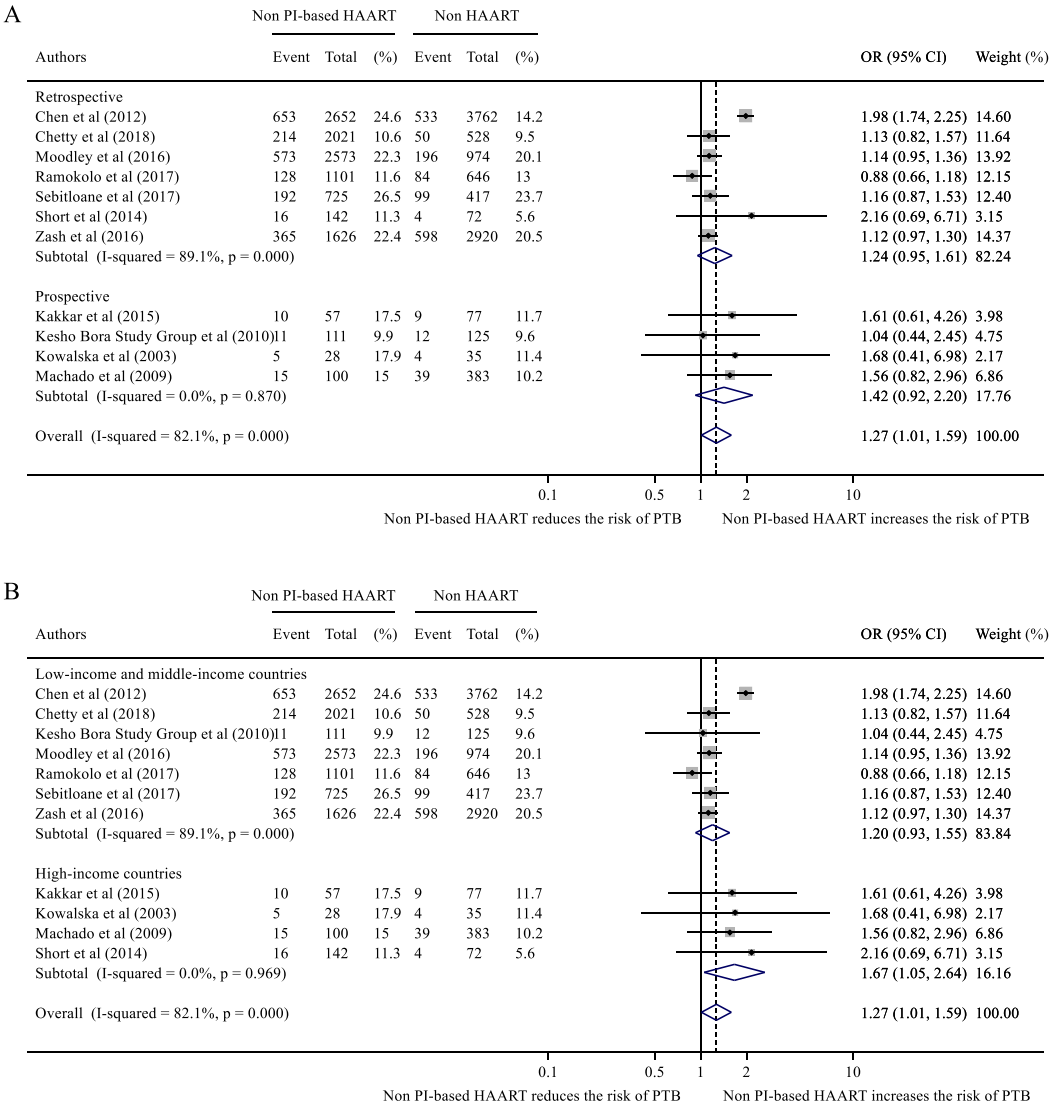


Figure 3.36. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with non PI-based HAART versus non HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

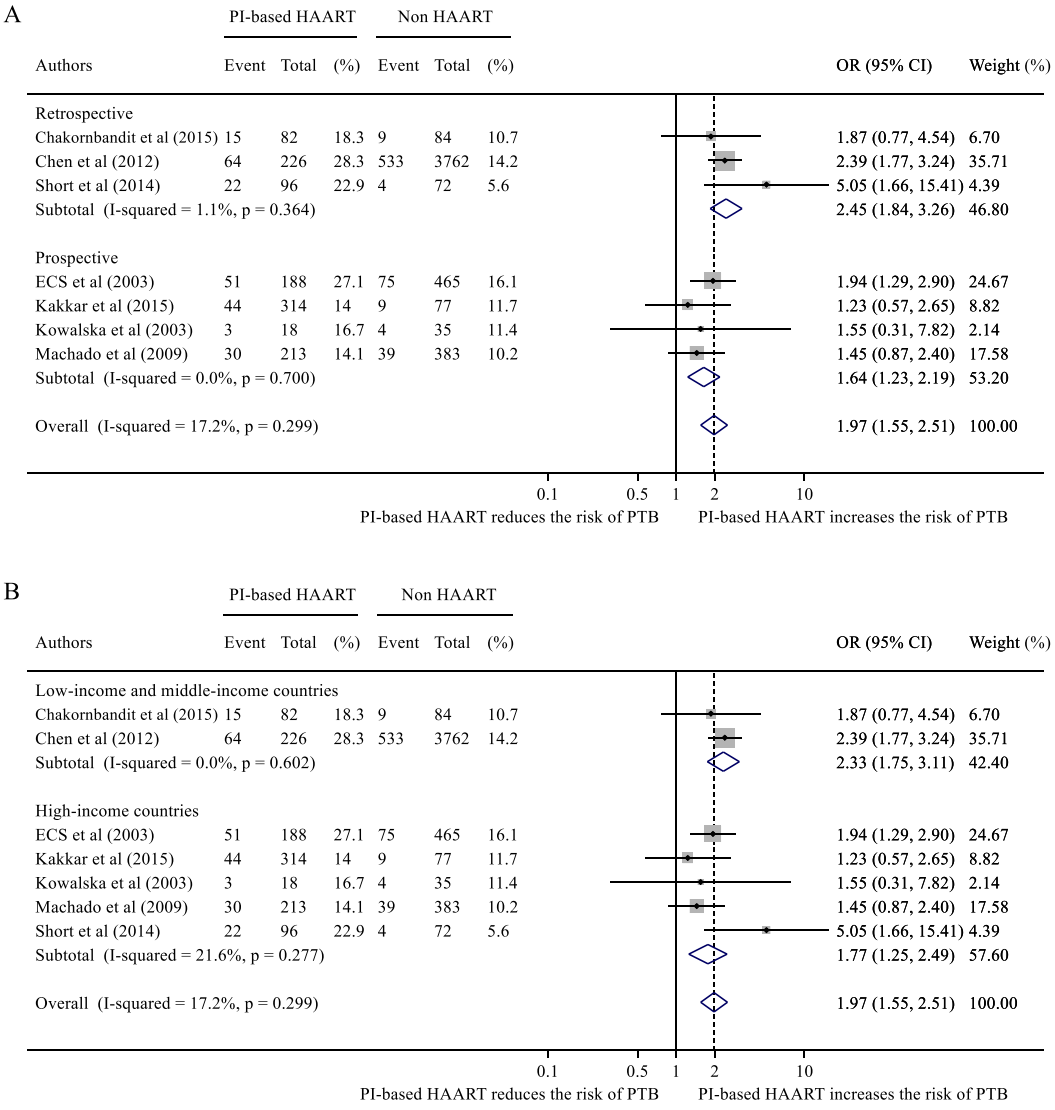


Figure 3.37. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with PI-based HAART versus non HAART using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth.

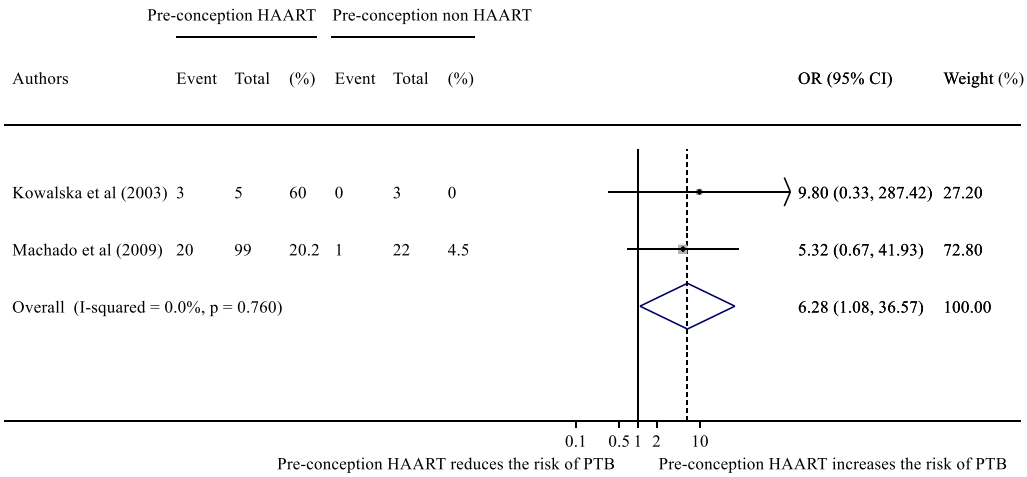


Figure 3.38. Forest plot of risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART initiated pre-conception using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

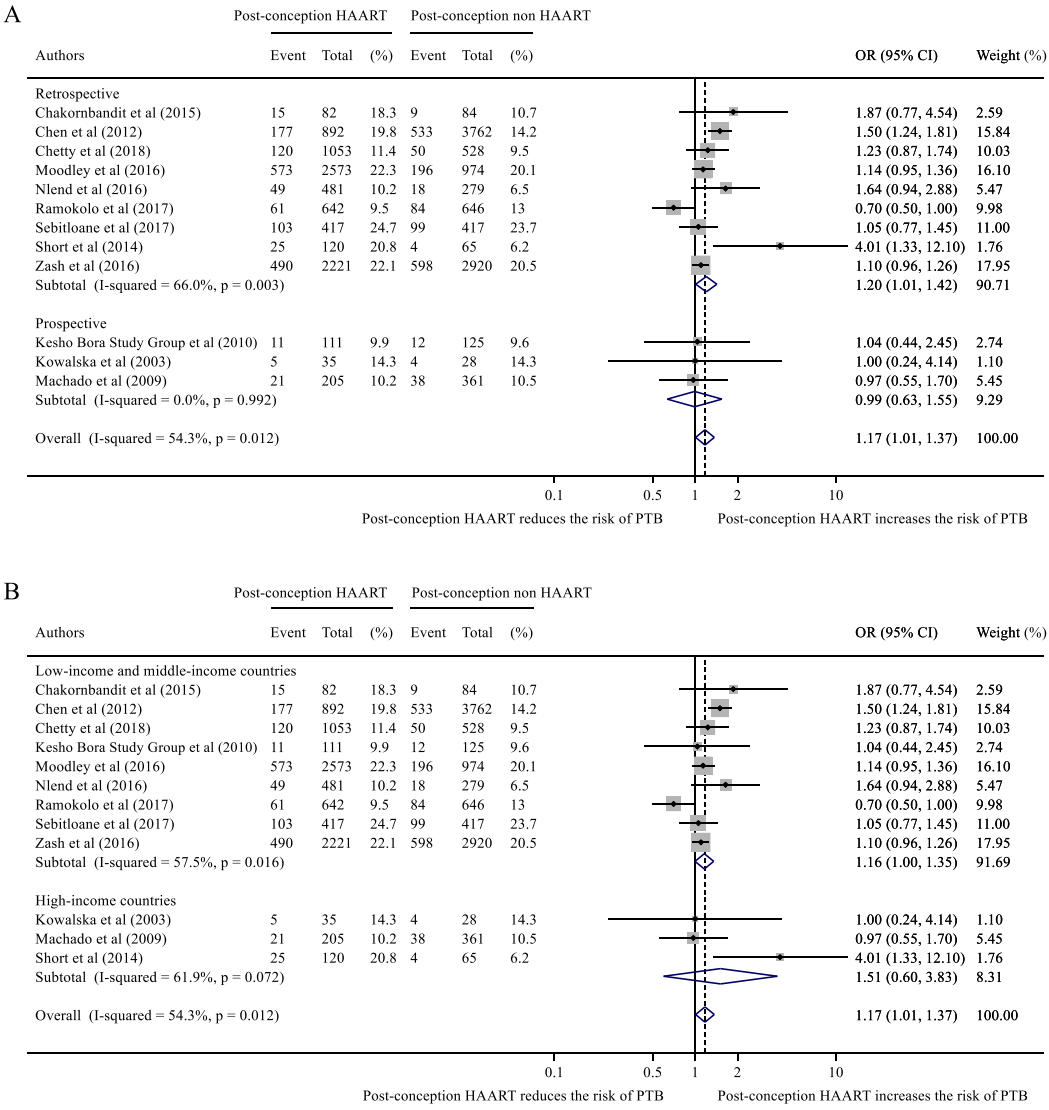


Figure 3.39. Forest plots of risk of preterm birth in HIV-positive pregnant women treated with HAART versus non HAART initiated post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Low birth weight

Combination therapy versus monotherapy

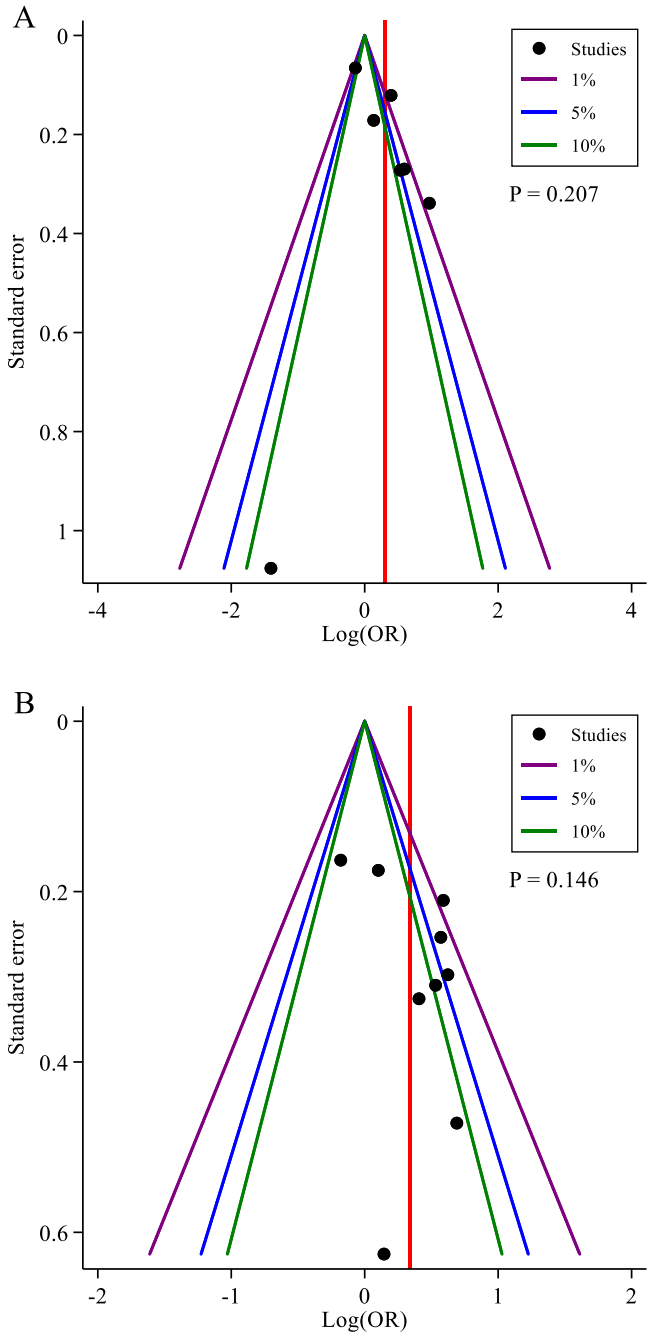


Figure 3.40. Contour-enhanced funnel plots of the cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by cohort design: retrospective, n=7 (A) and prospective, n=9 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

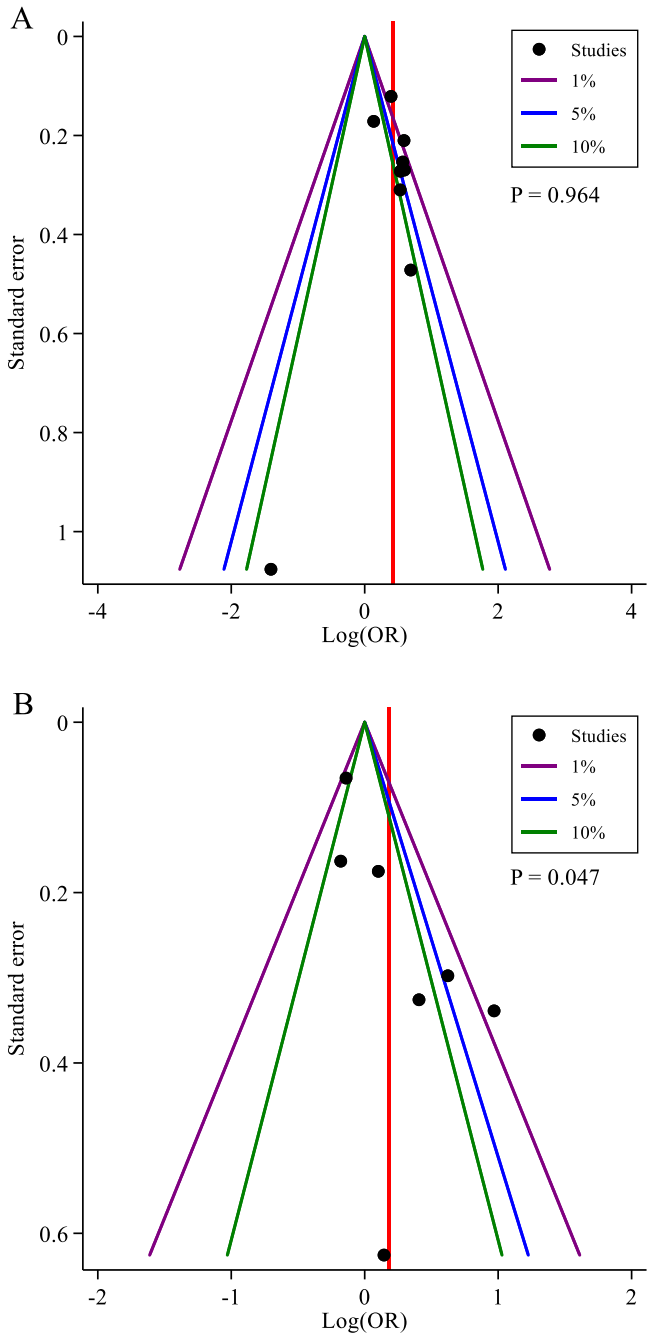


Figure 3.41. Contour-enhanced funnel plots of the cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with combination therapy versus monotherapy using unadjusted data, by country-income status: low and middle-income, n=9 (A) and high-income, n=7 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

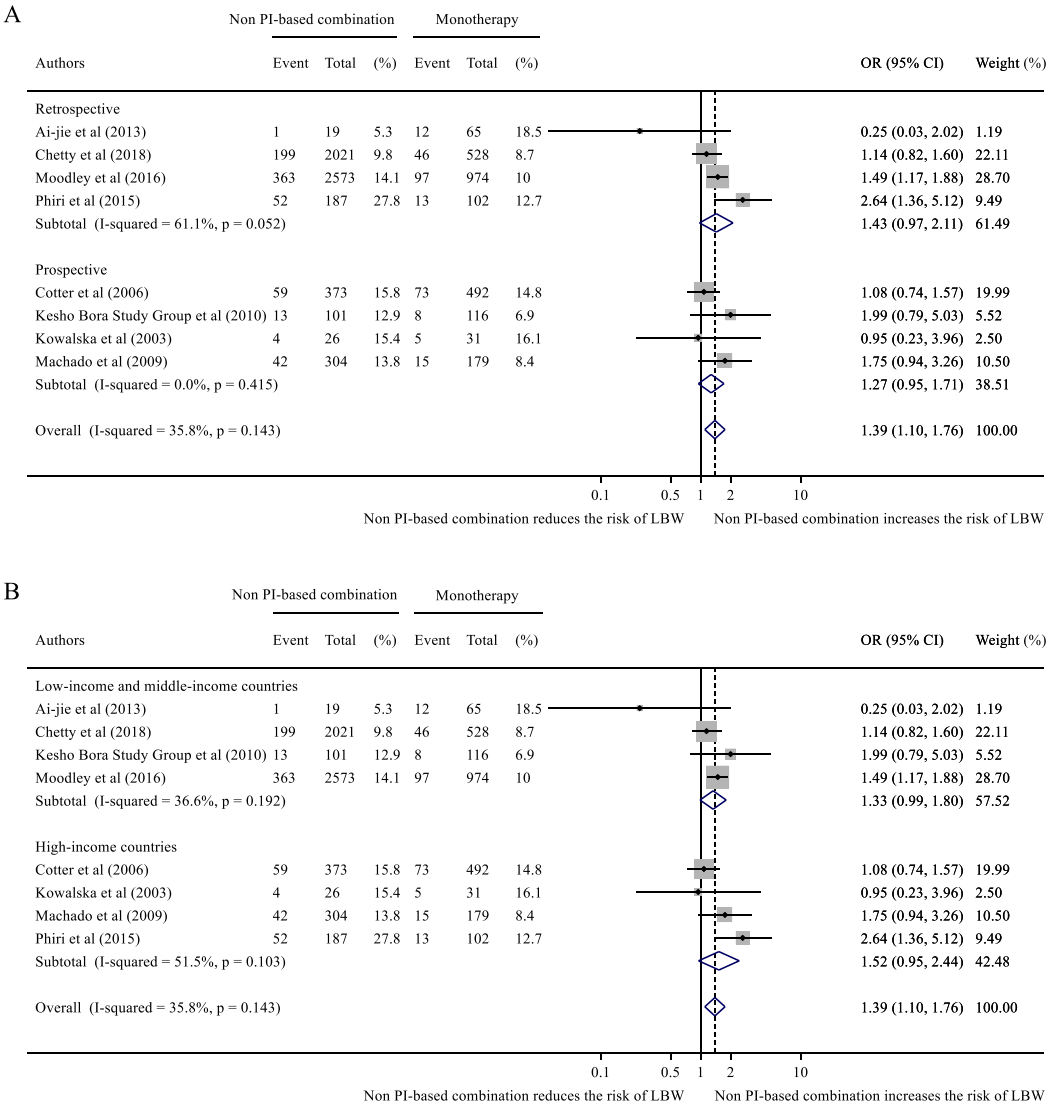


Figure 3.42. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non PI-based combination therapy versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

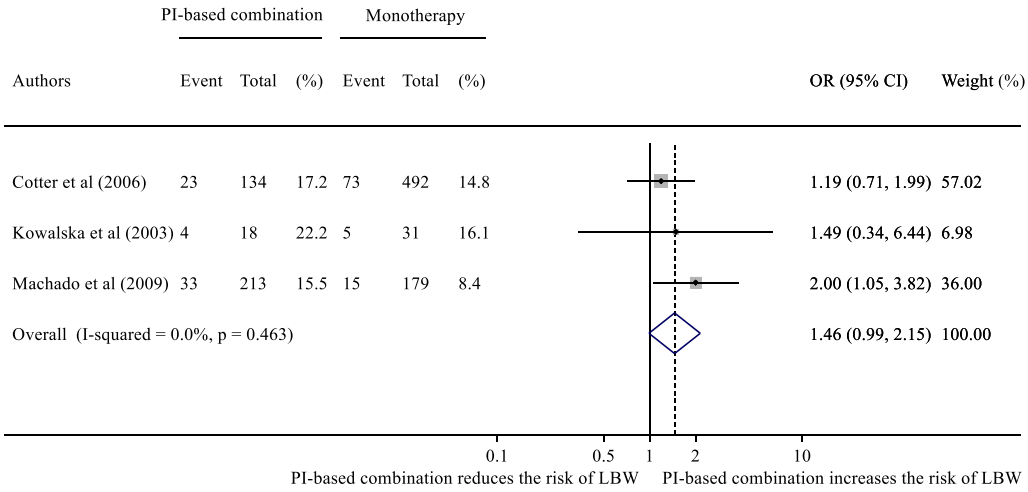


Figure 3.43. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with PI-based combination therapy versus monotherapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

HAART versus monotherapy

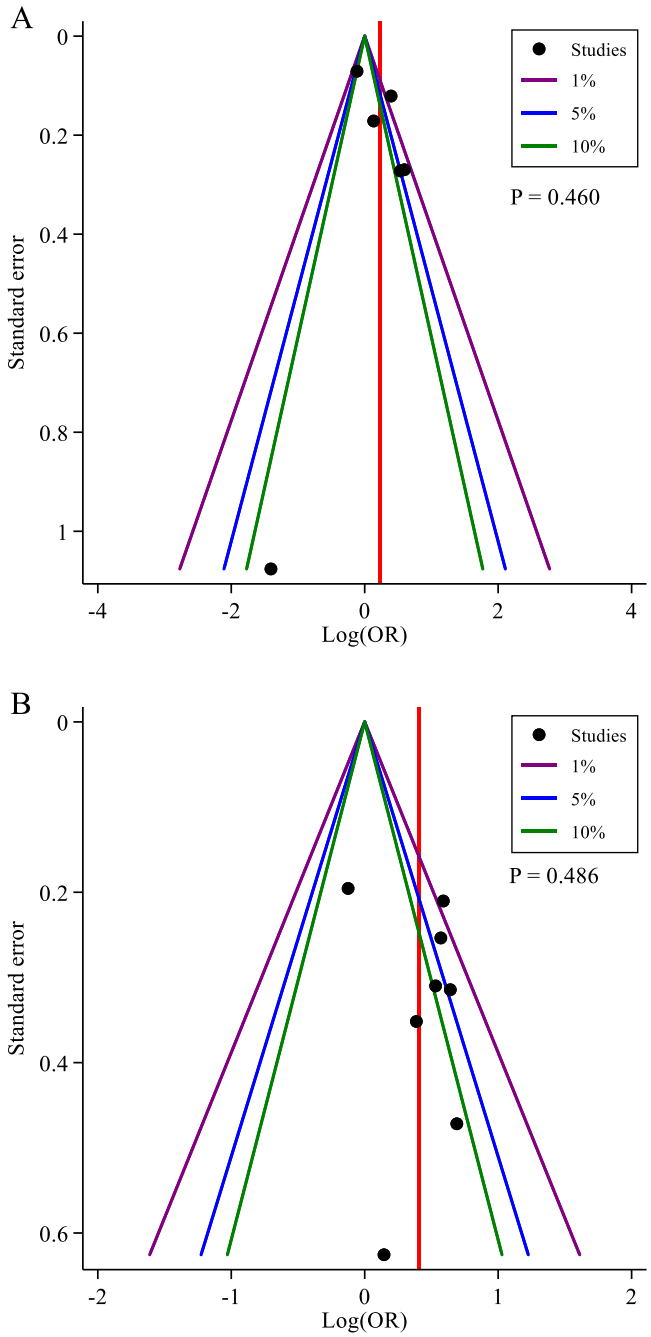


Figure 3.44. Contour-enhanced funnel plots of the cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data, by cohort design: retrospective, n=6 (A) and prospective, n=8 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

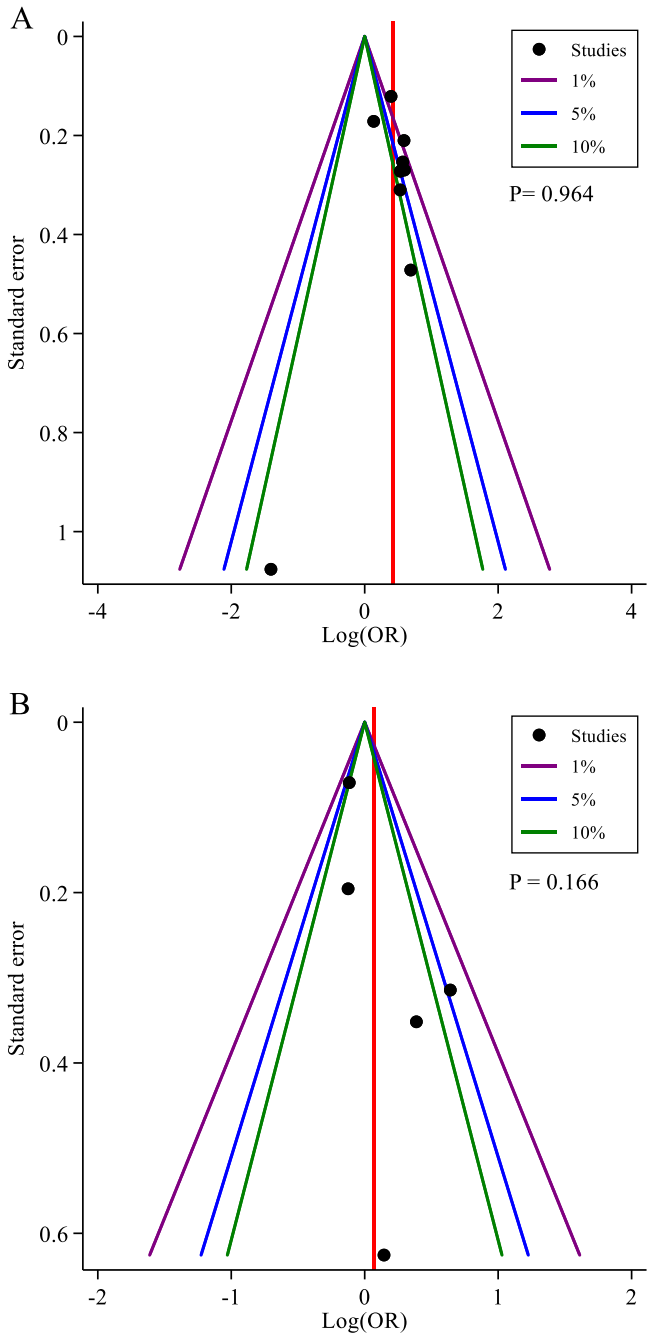


Figure 3.45. Contour-enhanced funnel plots of the cohorts comparing the risk of low birth weight in HIV-positive pregnant women treated with HAART versus monotherapy using unadjusted data, by country-income status: low and middle-income, n=9 (A) and high-income, n=5 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

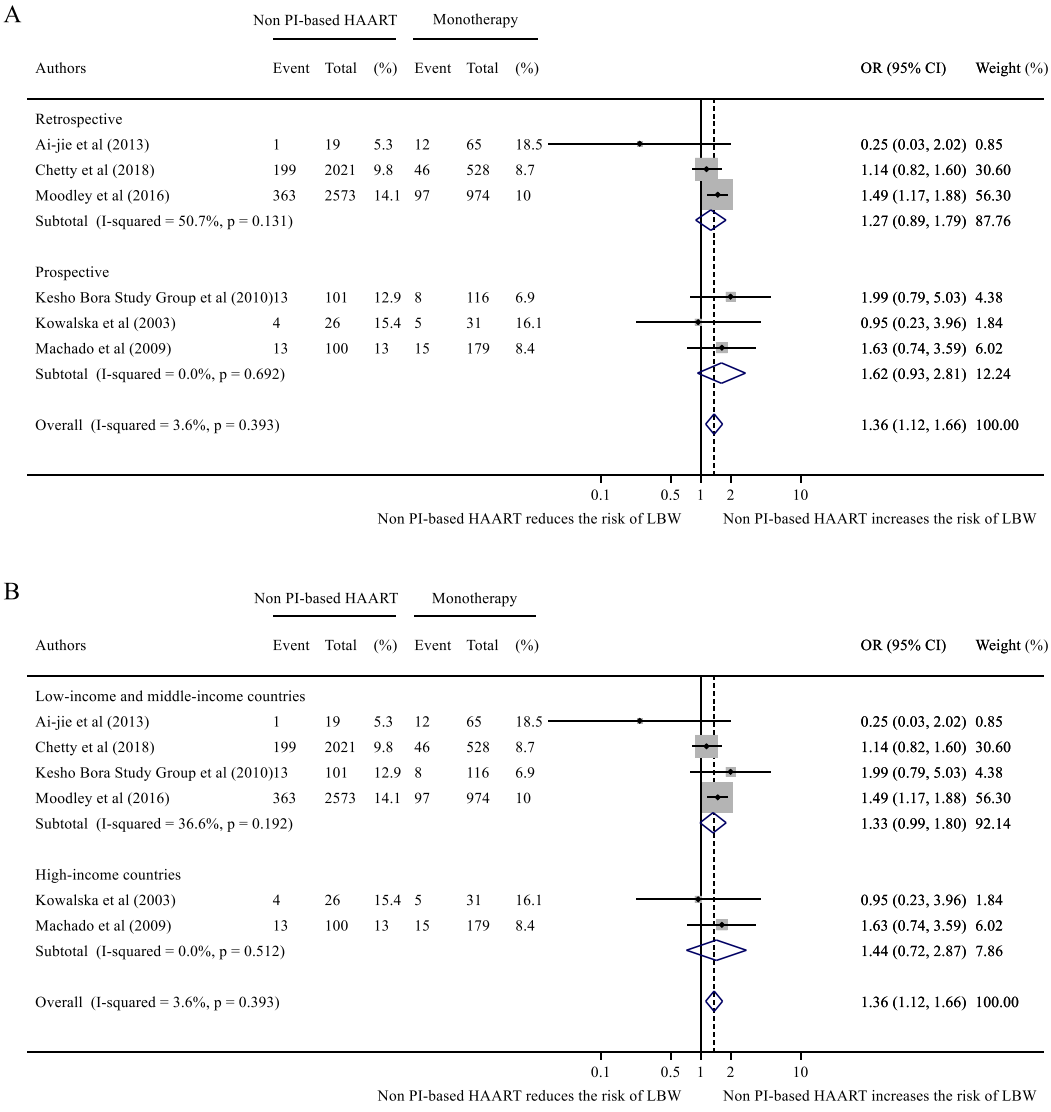


Figure 3.46. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non PI-based HAART versus monotherapy using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

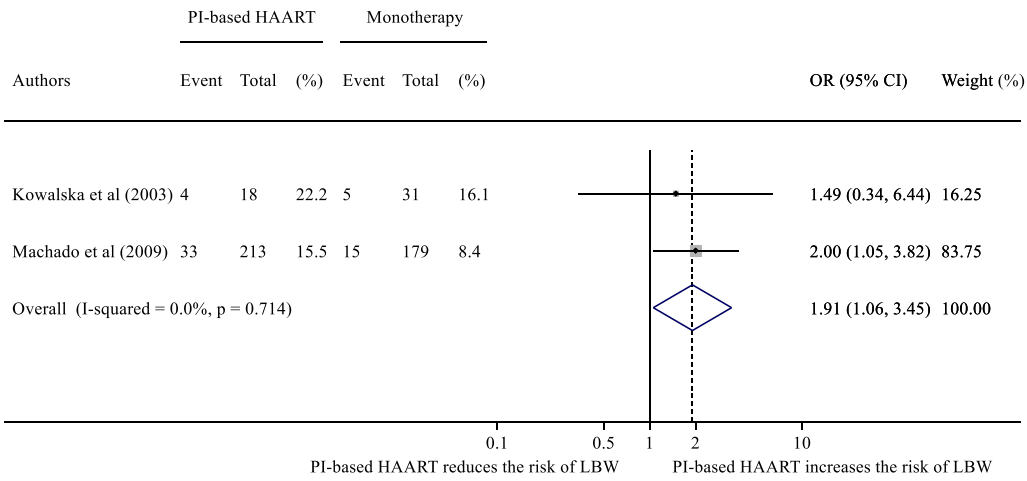
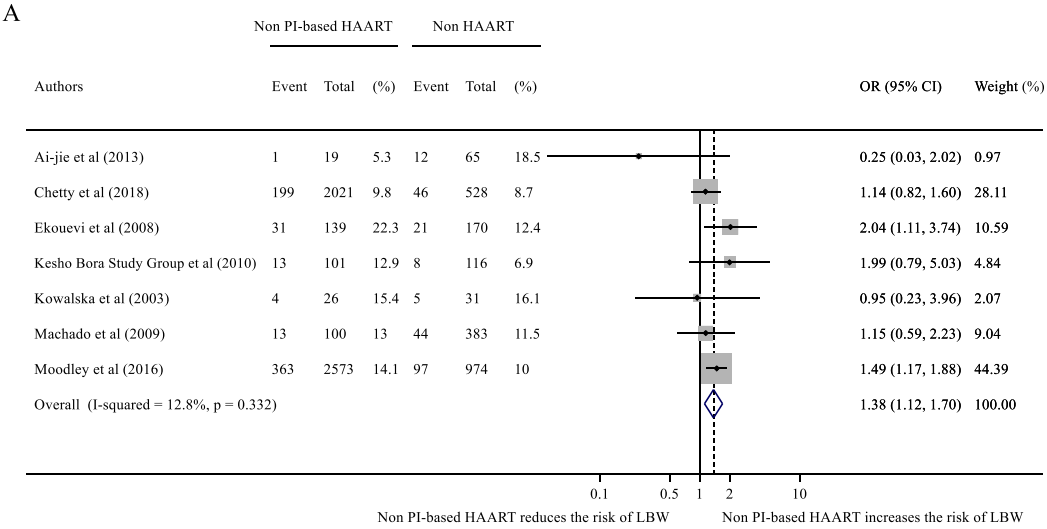


Figure 3.47. Forest plot of risk of low birth weight in HIV-positive pregnant women treated with PI-based HAART versus monotherapy using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

HAART versus non HAART

A



B

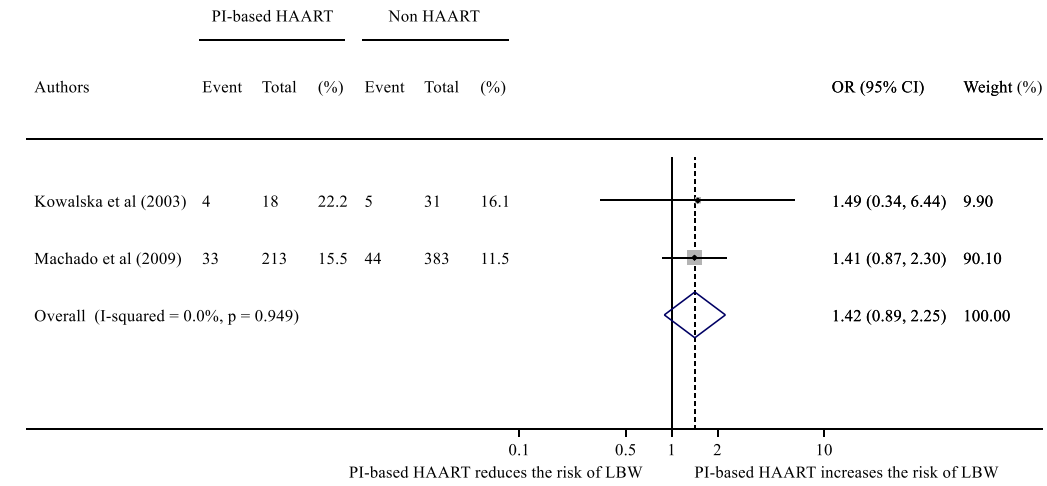


Figure 3.48. Forest plots of risk of low birth weight in HIV-positive pregnant women treated with non PI (A) or PI-based HAART (B) versus non HAART using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio; PI, protease inhibitor.

Table 3.6. Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes using unadjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Combination therapy versus monotherapy	PTB	22	1.29 (1.13, 1.48)	78.9	13	1.33 (1.12, 1.58)	85.2	9	1.23 (0.99, 1.53)	53.9	12	1.29 (1.06, 1.56)	82	10	1.29 (1.07, 1.55)	70.7
	VPTB	1	7.34 (0.41, 131.65)	–												
	LBW	16	1.39 (1.14, 1.70)	71.7	7	1.36 (0.98, 1.90)	81.9	9	1.40 (1.10, 1.79)	47.9	9	1.52 (1.31, 1.75)	0	7	1.20 (0.90, 1.59)	69.2
	VLBW	2	2.34 (1.11, 4.91)	0												
	SGA	6	1.14 (1.04, 1.25)	0							4	1.15 (1.03, 1.28)	4.9	2	1.10 (0.81, 1.51)	18
	MTCT	6	0.17 (0.09, 0.32)	36.7	2	0.19 (0.08, 0.43)	6.4	4	0.18 (0.07, 0.47)	55.3	3	0.16 (0.03, 0.85)	67.3	3	0.21 (0.12, 0.34)	0
Dual therapy versus monotherapy	PTB	8	0.99 (0.80, 1.23)	51.1	4	1.09 (0.74, 1.61)	75.5	4	0.95 (0.74, 1.21)	0						
	LBW	5	1.32 (0.80, 2.17)	79.3	2	1.60 (0.39, 6.46)	92.4	3	1.22 (0.67, 2.23)	61.8						
	SGA	2	1.30 (0.69, 2.43)	68.4												
	MTCT	2	0.27 (0.16, 0.48)	0												
HAART versus monotherapy	PTB	21	1.31 (1.15, 1.49)	77.4	12	1.33 (1.12, 1.57)	84.2	9	1.27 (1.01, 1.61)	55.9	12	1.29 (1.06, 1.56)	82	9	1.33 (1.10, 1.60)	67.8
	LBW	14	1.38 (1.12, 1.70)	67.3	6	1.26 (0.92, 1.71)	78.1	8	1.50 (1.17, 1.91)	27.9	9	1.52 (1.31, 1.75)	0	5	1.07 (0.81, 1.41)	46.1
	SGA	4	1.15 (1.03, 1.28)	4.9												
	VSGA	1	1.76 (1.39, 2.22)	–												
	Stillbirth	1	1.84 (1.41, 2.41)	–												
	MTCT	5	0.12 (0.05, 0.30)	34.9							3	0.16 (0.03, 0.85)	67.3	2	0.10 (0.03, 0.30)	0

Table 3.6. Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Non PI-based HAART versus monotherapy	PTB	11	1.24 (0.99, 1.55)	81.9	7	1.23 (0.95, 1.60)	89.1	4	1.26 (0.83, 1.93)	0	8	1.21 (0.95, 1.54)	87.2	3	1.49 (0.84, 2.65)	0
	LBW	6	1.36 (1.12, 1.66)	3.6	3	1.27 (0.89, 1.79)	50.7	3	1.62 (0.93, 2.81)	0	4	1.33 (0.99, 1.80)	36.6	2	1.44 (0.72, 2.87)	0
PI-based HAART versus monotherapy	PTB	7	1.93 (1.49, 2.50)	21.3	3	2.43 (1.84, 3.21)	0	4	1.60 (1.18, 2.16)	0	3	1.87 (1.20, 2.91)	48.2	4	1.91 (1.25, 2.90)	17.6
	LBW	2	1.91 (1.06. 3.45)	0												
HAART versus dual therapy	PTB	7	1.37 (1.22, 1.53)	0	3	1.34 (1.18, 1.53)	0	4	1.42 (1.02, 1.96)	44.3						
	LBW	4	1.08 (0.92, 1.28)	0												
	MTCT	1	0.31 (0.08, 1.22)	–												
HAART versus non HAART	PTB	25	1.35 (1.21, 1.51)	70.2	14	1.35 (1.17, 1.55)	79.4	11	1.36 (1.12, 1.64)	43.2	13	1.28 (1.06, 1.55)	80.5	12	1.39 (1.24, 1.57)	39.6
	sPTB	3	1.17 (0.81, 1.68)	0												
	VPTB	2	1.84 (0.74, 4.55)	54.3												
	LBW	16	1.34 (1.13, 1.60)	59.6	6	1.27 (0.96, 1.69)	74.7	10	1.40 (1.14, 1.71)	26	10	1.54 (1.34, 1.78)	0	6	0.97 (0.87, 1.09)	0
	SGA	5	1.15 (1.04, 1.27)	0												
	VSGA	2	1.36 (0.67, 2.76)	62.2												
	Stillbirth	2	1.88 (1.45, 2.42)	0												
	NND	1	2.22 (0.50, 9.76)	–												
	MTCT	6	0.11 (0.05, 0.27)	35.4	2	0.04 (0.01, 0.23)	0	4	0.15 (0.05, 0.44)	48.9	3	0.16 (0.03, 0.85)	67.3	3	0.09 (0.03, 0.26)	0

Table 3.6. Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Non PI-based HAART versus non HAART	PTB	11	1.27 (1.01, 1.59)	82.1	7	1.24 (0.95, 1.61)	89.1	4	1.42 (0.92, 2.20)	0	7	1.20 (0.93, 1.55)	89.1	4	1.67 (1.05, 2.64)	0
	LBW	7	1.38 (1.12, 1.70)	12.8	3	1.27 (0.89, 1.79)	50.7	4	1.58 (1.07, 2.32)	0	5	1.42 (1.08, 1.88)	36.1	2	1.11 (0.61, 2.03)	0
PI-based HAART versus non HAART	PTB	7	1.97 (1.55, 2.51)	17.2	3	2.45 (1.84, 3.26)	1.1	4	1.64 (1.23, 2.19)	0	2	2.33 (1.75, 3.11)	0	5	1.77 (1.25, 2.49)	21.6
	LBW	2	1.42 (0.89, 2.25)	0												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; MTCT, mother-to-child transmission; NND, neonatal death; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Table 3.7. Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes using adjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Combination therapy versus monotherapy	LBW	5	1.29 (1.02, 1.63)	4.5	3	1.35 (1.06, 1.71)	0	2	1.00 (0.43, 2.31)	40.2						
Dual therapy versus monotherapy	PTB	4	0.99 (0.69, 1.43)	67.7												
	MTCT	1	0.22 (0.10, 0.49)	–												
HAART versus monotherapy	PTB	10	1.38 (1.09, 1.76)	74.4	6	1.34 (0.97, 1.85)	77.6	4	1.50 (0.94, 2.38)	76.5	5	1.17 (0.80, 1.72)	69.3	5	1.60 (1.14, 2.25)	78
	LBW	4	1.36 (1.08, 1.72)	0												
	SGA	3	1.43 (1.19, 1.71)	0												
HAART versus dual therapy	PTB	1	1.21 (1.04, 1.40)	–												
HAART versus non HAART	PTB	12	1.35 (1.11, 1.64)	70.8	7	1.30 (1.03, 1.65)	75.3	5	1.53 (0.97, 2.39)	70	5	1.17 (0.80, 1.72)	69.3	7	1.49 (1.16, 1.91)	74.2
	VPTB	1	2.63 (1.30, 5.33)	–												
	LBW	5	1.42 (1.13, 1.78)	0	3	1.35 (1.06, 1.71)	0	2	2.27 (1.11, 4.65)	0						
	Stillbirth	1	2.27 (0.96, 5.39)	–												
NRTI-based HAART versus non HAART	PTB	1	1.04 (0.50, 2.14)	–												
	sPTB	1	0.88 (0.34, 2.29)	–												
	SGA	1	1.45 (0.43, 4.89)	–												

Table 3.7. Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes using adjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
NNRTI-based HAART versus non HAART	PTB	4	0.85 (0.66, 1.11)	0												
	sPTB	1	1.53 (0.62, 3.81)	–												
	SGA	3	1.34 (1.02, 1.78)	0												
PI-based HAART versus non HAART	PTB	3	1.22 (1.06, 1.41)	0												
	sPTB	1	1.41 (0.66, 2.99)	–												
	SGA	1	1.79 (0.64, 5.02)	–												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; MTCT, mother-to-child transmission; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VPTB, very PTB.

Summary of meta-analysis results for the effect of ART complexity on perinatal outcomes

Preterm birth (PTB)

Combination therapy versus monotherapy

The overall meta-analysis of unadjusted effect estimates, including 22 cohorts and 55,179 women, showed that combination therapy (dual therapy, HAART) was associated with an approximately 30% increase in the odds of having a preterm baby compared with monotherapy. The association remained across cohort design and country income status (Table 3.6). All these associations were statistically significant, except for the sub-group analysis of prospective cohorts, which was borderline significant. The I^2 values indicated a high degree of heterogeneity in most of these analyses (Table 3.6).

When combination therapy was restricted to dual therapy, there was no association between dual therapy and PTB compared with monotherapy (Table 3.6). However, when combination therapy was restricted to HAART, there was an association between HAART and an increased risk of PTB compared with monotherapy; the association was consistently observed across cohort design and country-income status (Table 3.6). According to HAART class, non PI had a borderline significant association; however, PI showed a significant association with an increased risk of PTB compared with monotherapy (Table 3.6).

In the meta-analysis of adjusted effect estimates, dual therapy was not associated with PTB; however, HAART was associated with a 38% increase in the odds of having a preterm baby compared with monotherapy (Table 3.7).

HAART versus dual therapy

The pooled unadjusted effect estimates, including seven cohorts and 20,103 women, revealed an association between HAART and a 37% increase in the odds of having a preterm baby compared with dual therapy. The association persisted across cohort design (Table 3.6).

HAART versus non HAART

The overall meta-analysis of unadjusted effect estimates, including 25 cohorts and 57,229 women, suggested that HAART was associated with a 35% increase in the odds of having a preterm baby compared with non HAART (monotherapy, dual therapy) (Table 3.6). The association was consistently observed across cohort design and country-income status, and was irrespective of HAART class (non PI and PI). PI (OR = 1.97) showed a 70% higher OR than non PI-based HAART (OR = 1.27) (Table 3.6).

In the meta-analysis of adjusted effect estimates, including 12 cohorts, the association between HAART and an increased risk of PTB remained with the same OR as observed in the meta-analysis of unadjusted effect estimates (OR = 1.35) (Table 3.7). The association persisted in the sub-group analysis of retrospective cohorts (but not prospective), and in the sub-group analysis of cohorts conducted in high-income countries (but not in LMICs) (Table 3.7). Among NRTI, NNRTI and PI-based HAART, only PI showed a significant association with a 22% increase in the odds of having a preterm baby compared with non HAART (Table 3.7).

Spontaneous preterm birth (sPTB)

HAART versus non HAART

Only three cohorts were available for the meta-analysis of unadjusted effect estimates, i.e. there was insufficient evidence to show a difference in sPTB risk between HAART and non HAART (Table 3.6).

Very preterm birth (VPTB)

HAART versus non HAART

The pooled unadjusted effect estimates including two cohorts indicated there was insufficient evidence to show an association between HAART and VPTB compared with non HAART (Table 3.6).

Low birth weight (LBW)

Combination therapy versus monotherapy

From the synthesis of unadjusted effect estimates of 16 cohorts involving 19,054 women, combination therapy was associated with nearly a 40% increase in the odds of having a LBW baby compared with monotherapy (Table 3.6). In sub-group analyses by cohort design, the association remained in prospective, but not retrospective cohorts; by country-income status, the association remained in LMIC, but not high-income country (Table 3.6).

When combination therapy was limited to dual therapy, there was no association between dual therapy and LBW compared with monotherapy (Table 3.6). However, when combination therapy was limited to HAART, there was an association between HAART and a higher risk of LBW compared with monotherapy. The association remained in the sub-group analysis of prospective

cohorts (but not retrospective), and in the sub-group analysis of LMIC (but not high-income country) (Table 3.6). The association persisted irrespective of HAART class, and PI (OR = 1.91) showed a 55% higher OR than non PI (OR = 1.36) (Table 3.6).

Five cohorts were included in the meta-analysis of adjusted effect estimates, and showed that combination therapy was associated with a nearly 30% increase in the odds of having a LBW baby compared with monotherapy (Table 3.7). The finding remained when combination therapy was restricted to HAART – the odds of having a LBW baby on HAART were 36% higher than monotherapy (Table 3.7).

HAART versus dual therapy

Four cohorts, including 4,653 women, were available for the meta-analysis of unadjusted effect estimates, and revealed that there was insufficient evidence to show a difference in LBW risk between HAART and dual therapy (Table 3.6).

HAART versus non HAART

The meta-analysis of unadjusted effect estimates, including 16 cohorts and 18,296 women, showed that the odds of having a LBW baby on HAART were 34% higher than on non HAART (Table 3.6). In sub-group analyses by cohort design, the finding remained in prospective, but not retrospective cohorts; by country-income status, the finding remained in LMIC, but not in high-income country (Table 3.6). According to HAART class, non PI was associated with an almost 40% increase in the odds of having a LBW baby compared with non HAART; however, the association was not observed in PI, which was tested in only two of the cohorts included in the analysis (Table 3.6).

The pooled adjusted effect estimates, including five cohorts, showed that HAART remained associated with a higher risk of LBW compared with non HAART (OR = 1.42) (Table 3.7). The association was consistently observed across cohort design, with OR = 1.35 and OR = 2.27 for retrospective and prospective cohorts, respectively; however, very few studies were included in these two sub-group analyses (Table 3.7).

Very low birth weight (VLBW)

Combination therapy versus monotherapy

Only two cohorts were included in the meta-analysis of unadjusted effect estimates, which showed that women receiving combination therapy were 2.34 times more likely to have a VLBW baby than those receiving monotherapy (Table 3.6).

Small for gestational age (SGA)

Combination therapy versus monotherapy

The pooled unadjusted effect estimates of 6 cohorts, involving 15,487 women, revealed that combination therapy was associated with a 14% increase in the odds of having an SGA baby compared with monotherapy (Table 3.6). When combination therapy was limited to dual therapy, there was no association between dual therapy and SGA compared with monotherapy (Table 3.6). However, when combination therapy was limited to HAART, there was an association between HAART and a 15% increase in the odds of having an SGA baby compared with monotherapy. However, few studies ($n<5$) were included in these two sensitivity analyses (Table 3.6).

Only three cohorts were available for the meta-analysis of adjusted effect estimates, which showed that HAART remained associated with an increased risk of SGA (with a 43% increase in the odds of having an SGA baby) compared with monotherapy (Table 3.7).

HAART versus non HAART

The meta-analysis of unadjusted effect estimates, including 5 cohorts and 15,632 women, showed that HAART was associated with a 15% increase in the odds of having an SGA baby compared with non HAART (a similar finding to that observed for "HAART versus monotherapy", see above) (Table 3.6).

The pooled adjusted effect estimates including three cohorts revealed that NNRTI-based HAART was associated with a 34% increase in the odds of having an SGA baby compared with non HAART (Table 3.7).

Very small for gestational age (VSGA)

HAART versus non HAART

Only two cohorts were available for the meta-analysis of unadjusted effect estimates, and there was insufficient evidence to show a difference in VSGA risk between HAART and non HAART (Table 3.6).

Stillbirth

HAART versus non HAART

The meta-analysis of unadjusted effect estimates showed that the odds of having a stillbirth on HAART were 88% higher than in women on non HAART; however, only two cohorts were included in this analysis (Table 3.6).

Mother-to-child transmission (MTCT)

Combination therapy versus monotherapy

Six cohorts, involving 4,240 women, were included in the meta-analysis of unadjusted effect estimates, which showed that the odds of MTCT in women receiving combination therapy were reduced by 83% compared with those receiving monotherapy (Table 3.6). The finding was consistently observed across cohort design and country income status (Table 3.6). Both dual therapy and HAART were associated with a reduced risk of MTCT compared with monotherapy; the effect of HAART (OR = 0.12) on the reduction of MTCT risk was 15% higher than dual therapy (OR = 0.27) (Table 3.6).

HAART versus non HAART

The pooled unadjusted effect estimates, including six cohorts and 3,431 women, showed that the odds of MTCT on HAART were approximately 90% less than on non HAART; this finding persisted across cohort design and country-income status (Table 3.6).

Appendix 3.10

Sensitivity analyses and summary of meta-analysis results: effect of ART class on adverse perinatal outcomes.

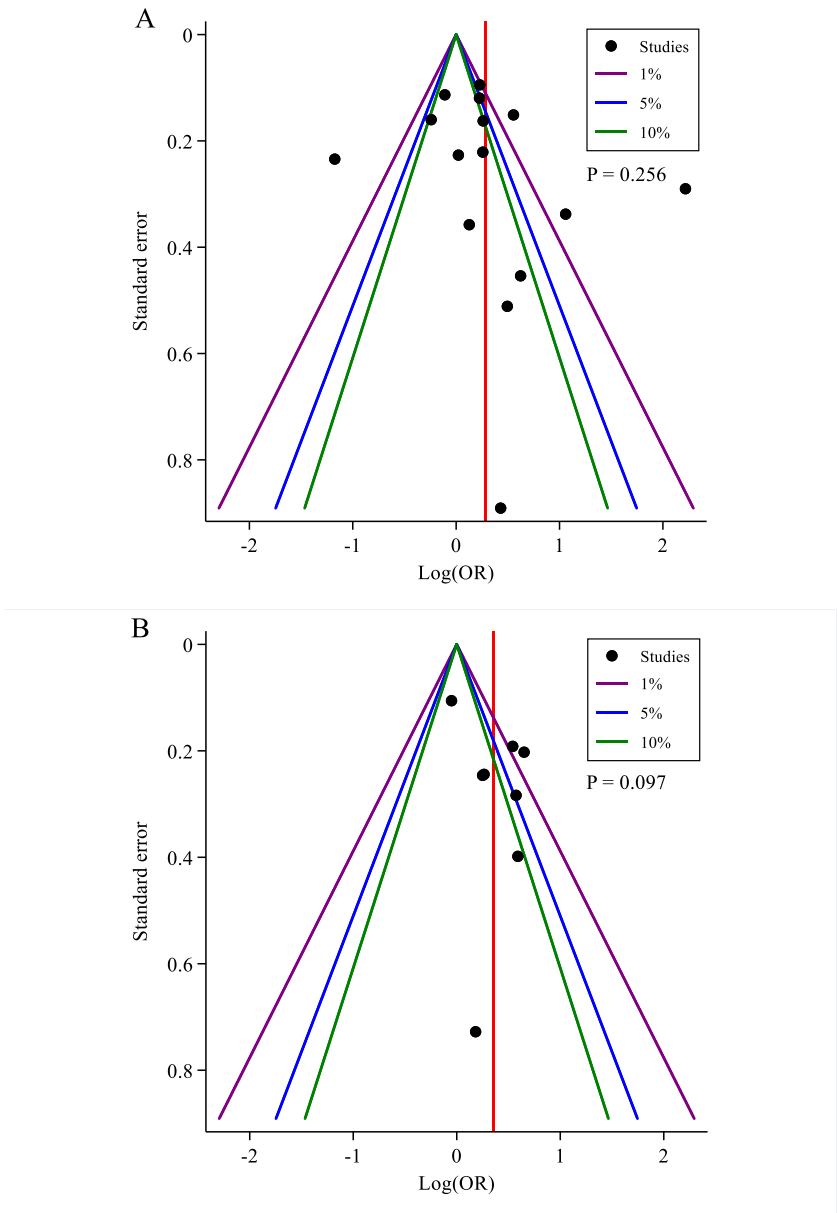


Figure 3.49. Contour-enhanced funnel plots of the cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by cohort design: retrospective, n=15 (A) and prospective, n=8 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

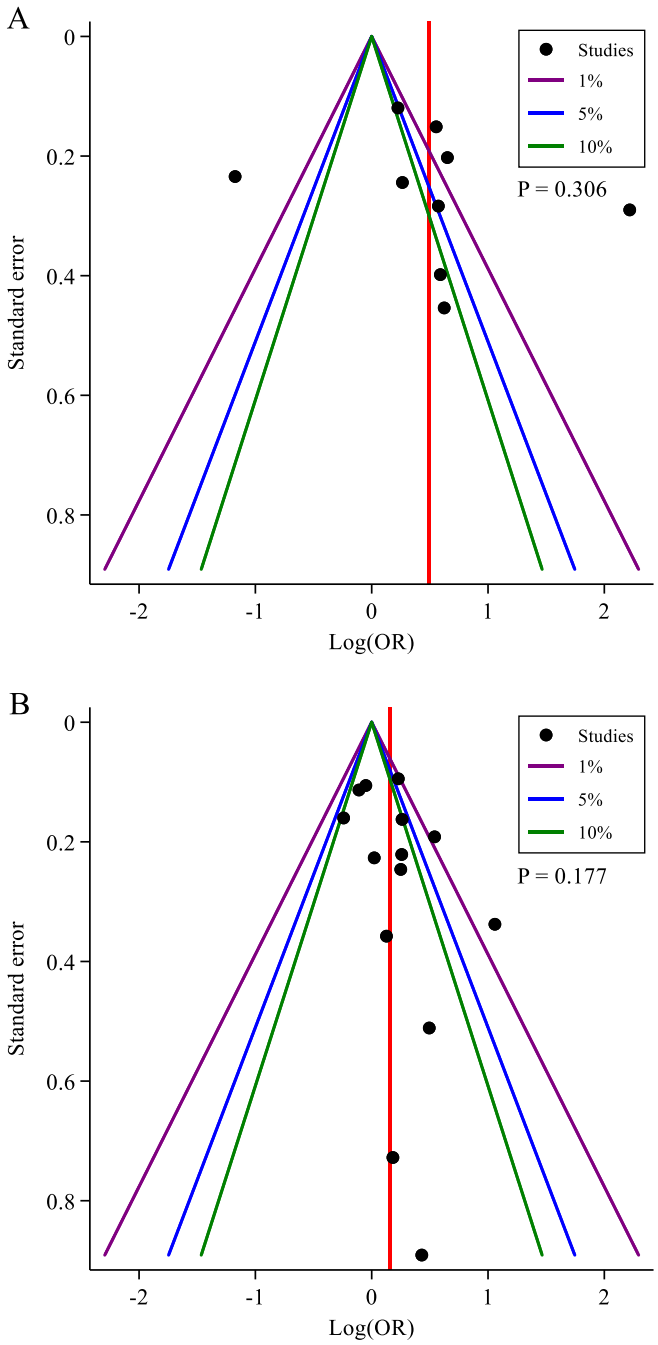


Figure 3.50. Contour-enhanced funnel plots of the cohorts comparing the risk of preterm birth in HIV-positive pregnant women treated with PI versus non PI-based regimens using unadjusted data, by country-income status: low and middle-income, n=9 (A) and high-income, n=14 (B). Solid black circles correspond to the cohorts. Solid red vertical line corresponds to the estimated summary log(OR). Solid purple, blue and green lines correspond to the contours of statistical significance of 0.01, 0.05 and 0.10 respectively. Abbreviations: HIV, human immunodeficiency virus; OR, odds ratio.

Table 3.8. Summary of meta-analysis results for the effect of ART class on perinatal outcomes using unadjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
PI versus non PI-based regimens	PTB	23	1.36 (1.11, 1.67)	82.9	15	1.33 (1.00, 1.77)	87.5	8	1.43 (1.11, 1.83)	57	9	1.63 (0.99, 2.66)	91.2	14	1.17 (1.00, 1.37)	53.4
	VPTB	6	1.37 (0.90, 2.11)	25.3	4	1.33 (0.77, 2.31)	46.5	2	1.90 (0.70, 5.17)	0	3	1.51 (1.03, 2.21)	0	3	1.44 (0.52, 3.98)	59.6
	LBW	11	1.07 (0.85, 1.34)	61.5	5	0.83 (0.70, 0.97)	12.4	6	1.44 (1.15, 1.79)	0.2	5	1.23 (0.74, 2.03)	81.8	6	0.92 (0.79, 1.08)	0
	VLBW	6	0.81 (0.43, 1.52)	31.5	3	1.12 (0.38, 3.26)	67.4	3	0.55 (0.21, 1.46)	0	3	0.88 (0.21, 3.69)	36.3	3	0.76 (0.35, 1.63)	44.6
	SGA	10	1.19 (0.92, 1.54)	68.8	7	1.19 (0.87, 1.63)	78.9	3	1.23 (0.77, 1.97)	0	3	1.53 (0.80, 2.91)	84.7	7	0.97 (0.82, 1.15)	0
	Stillbirth	2	1.05 (0.73, 1.50)	0												
PI versus non PI-based HAART	PTB	18	1.26 (0.99, 1.59)	85.2	11	1.26 (0.91, 1.75)	90	7	1.26 (0.90, 1.77)	59.9	8	1.49 (0.86, 2.58)	92.3	10	1.07 (0.90, 1.26)	49.8
	sPTB	2	3.35 (0.46, 24.38)	96.9												
	VPTB	4	1.21 (0.75, 1.98)	32.9	2	1.07 (0.54, 2.12)	68.1	2	1.90 (0.70, 5.17)	0						
	LBW	8	0.90 (0.74, 1.09)	27.7	4	0.80 (0.66, 0.97)	23.2	4	1.26 (0.91, 1.76)	0	4	0.98 (0.61, 1.56)	65.8	4	0.88 (0.74, 1.06)	0
	VLBW	4	0.68 (0.29, 1.58)	32.5	2	0.90 (0.23, 3.60)	72.1	2	0.35 (0.07, 1.91)	0						
	SGA	8	1.34 (0.99, 1.81)	66.9	5	1.40 (0.94, 2.07)	80.7	3	1.23 (0.77, 1.97)	0	3	1.53 (0.80, 2.91)	84.7	5	1.07 (0.87, 1.32)	0
	VSGA	2	1.45 (1.08, 1.95)	0												
	Stillbirth	1	1.13 (0.67, 1.91)	–												
	NND	1	1.84 (0.97, 3.50)	–												
	MTCT	2	0.84 (0.45, 1.57)	0												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; LBW, low birth weight; MTCT, mother-to-child transmission; NND, neonatal death; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Table 3.9. Summary of meta-analysis results for the effect of ART class on perinatal outcomes using adjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
PI versus non PI-based regimens	PTB	7	1.19 (1.00, 1.42)	27	4	1.34 (1.12, 1.60)	0	3	0.99 (0.81, 1.21)	0	2	1.15 (0.85, 1.55)	0	5	1.22 (0.95, 1.57)	51.2
	sPTB	1	1.22 (0.70, 2.12)	–												
	LBW	2	1.11 (0.67, 1.84)	12.4												
	SGA	3	1.14 (0.73, 1.80)	81.4												
PI versus non PI-based HAART	PTB	4	1.21 (0.93, 1.59)	62.6	2	1.36 (1.02, 1.82)	48.2	2	0.98 (0.80, 1.21)	0						
	VPTB	1	1.38 (0.75, 2.61)	–												
	SGA	2	1.35 (0.82, 2.25)	82.4												
	VSGA	1	1.93 (1.29, 2.94)	–												
	Stillbirth	1	1.84 (0.94, 3.69)	–												
	NND	1	1.61 (0.56, 4.73)	–												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; LBW, low birth weight; NND, neonatal death; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VPTB, very PTB; VSGA, very SGA.

Summary of meta-analysis results for the effect of ART class on perinatal outcomes

Preterm birth (PTB)

The overall meta-analysis of unadjusted effect estimates, including 23 cohorts and 34,960 women, showed a 36% increase in the odds of having a preterm baby in HIV-positive women receiving PI compared with those receiving non PI-based regimens (Table 3.8). In sub-group analyses by cohort design and by country-income status, an association between PI and an increased risk of PTB remained in each sub-group but at borderline statistical significance, except for prospective cohorts, which showed a significant association (Table 3.8). The I^2 values indicated a high degree of heterogeneity in most of these analyses (Table 3.8).

In a sensitivity analysis limited to women on HAART, PI was associated with a 26% increase in the odds of having a preterm baby compared with non PI but at borderline statistical significance; a high degree of heterogeneity was evident (Table 3.8).

The pooled adjusted effect estimates, including seven cohorts and 12,790 women, showed a nearly 20% increase in the odds of having a preterm baby in HIV-positive women receiving PI compared with those receiving non PI-based regimens but at borderline statistical significance (Table 3.9). In the sub-group analysis of retrospective, but not prospective cohorts, this association became significant with a 34% increase in the odds of having a preterm baby in women receiving PI-based regimens compared with those receiving non PI-based regimens (Table 3.9). A sensitivity analysis restricted to women receiving

HAART did not show evidence for the association between PI and an increased risk of PTB (Table 3.9).

Spontaneous preterm birth (sPTB)

The pooled unadjusted effect estimates of two cohorts in which all 2,519 women were on HAART, showed no association between PI and sPTB (Table 3.8).

Very preterm bitrh (VPTB)

No difference in the risk of VPTB between PI and non PI-based regimens was shown by the meta-analysis of unadjusted effect estimates, including six cohorts and 9,348 women (Table 3.8). In sub-group analyses, the finding was consistently observed across cohort design and in the meta-analysis of high-income country cohorts (Table 3.8). However, the meta-analysis of three LMIC cohorts showed that women receiving PI were 1.51 times more likely to have a preterm baby than those receiving non PI-based regimens (Table 3.8). Sensitivity analyses restricted to women receiving HAART showed no association between PI and VPTB (Table 3.8).

Low birth weight (LBW)

The overall meta-analysis of unadjusted effect estimates, including 11 cohorts and 9,401 women, showed no association between PI-based regimens and LBW, with moderate heterogeneity (Table 3.8). The finding persisted across country-income status. In retrospective cohorts, PI-based regimens were associated with a 17% reduction in the odds of having a LBW baby; however, in prospective cohorts, PI-based regimens were associated with a 44% increase in the odds of having a LBW

baby compared with non PI-based regimens. No heterogeneity was observed in these two sub-groups (Table 3.8).

In a sensitivity analysis restricted to women on HAART, PI remained not associated with LBW. In retrospective cohorts, PI was consistently associated with a reduced risk of LBW; however, in prospective cohorts, the association between PI and an increased risk of LBW became non-significant (Table 3.8).

Only two cohorts were available for the meta-analysis of adjusted effect estimates, which did not show evidence of an association between PI-based regimens and LBW (Table 3.9).

Very low birth weight (VLBW)

The pooled unadjusted effect estimates of six cohorts, including 5,370 women, showed no association between PI-based regimens and VPTB. The finding remained across cohort design and country-income status, and in sensitivity analyses restricted to women treated with PI and non PI-based HAART (Table 3.8).

Small for gestational age (SGA)

The overall meta-analysis of unadjusted effect estimates, including 10 cohorts and 11,462 women, showed no difference in SGA risk between women on PI and those on non PI-based regimens. The finding persisted across cohort design and country-income status (Table 3.8). A sensitivity analysis limited to women on HAART revealed that the odds of having an SGA baby in women on PI were

reduced by 34% compared with those on non PI; however, the finding was at borderline statistical significance (Table 3.8).

In the meta-analysis of adjusted effect estimates of three cohorts, including 4,896 women, PI-based regimens were not associated with SGA. The finding persisted in the sensitivity analysis limited to women on PI and non PI-based HAART (Table 3.9).

Very small for gestational age (VSGA)

Only two cohorts, including 5,178 women, were available for the meta-analysis of unadjusted effect estimates, and showed that women on PI-based HAART were 1.45 times more likely to have an SGA baby than those on non PI-based HAART (Table 3.8).

Stillbirth

PI-based regimens were not associated with stillbirth; however, only two cohorts including 12,996 women, were included in this meta-analysis of unadjusted effect estimates (Table 3.8).

Mother-to-child transmission (MTCT)

The pooled unadjusted effect estimates of two cohorts, including 1,372 women, showed no association between PI-based HAART and MTCT of HIV (Table 3.8).

Appendix 3.11

Sensitivity analyses and summary of meta-analysis results: effect of timing of ART initiation on adverse perinatal outcomes.

Preterm birth

Pre-conception versus post-conception

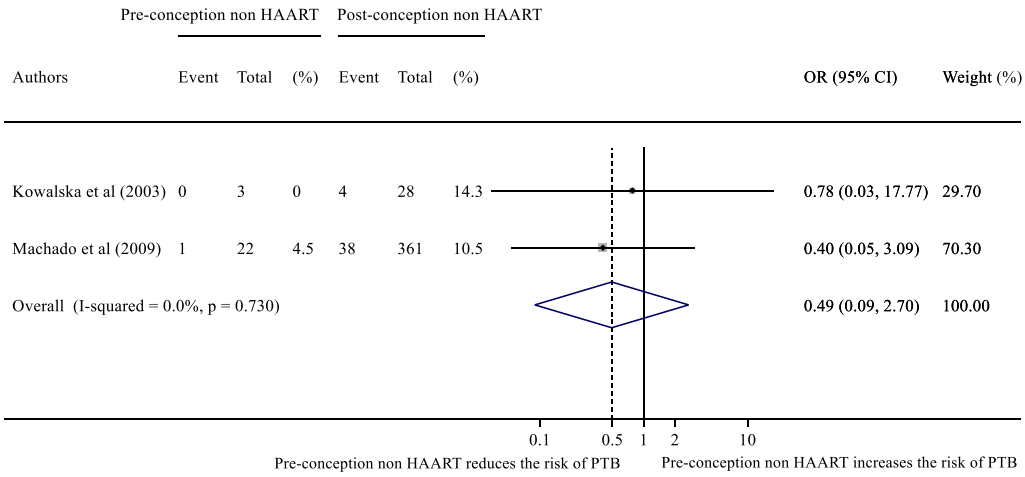


Figure 3.51. Forest plot of risk of preterm birth in HIV-positive pregnant women who initiated treatment (non HAART) pre-conception versus post-conception using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

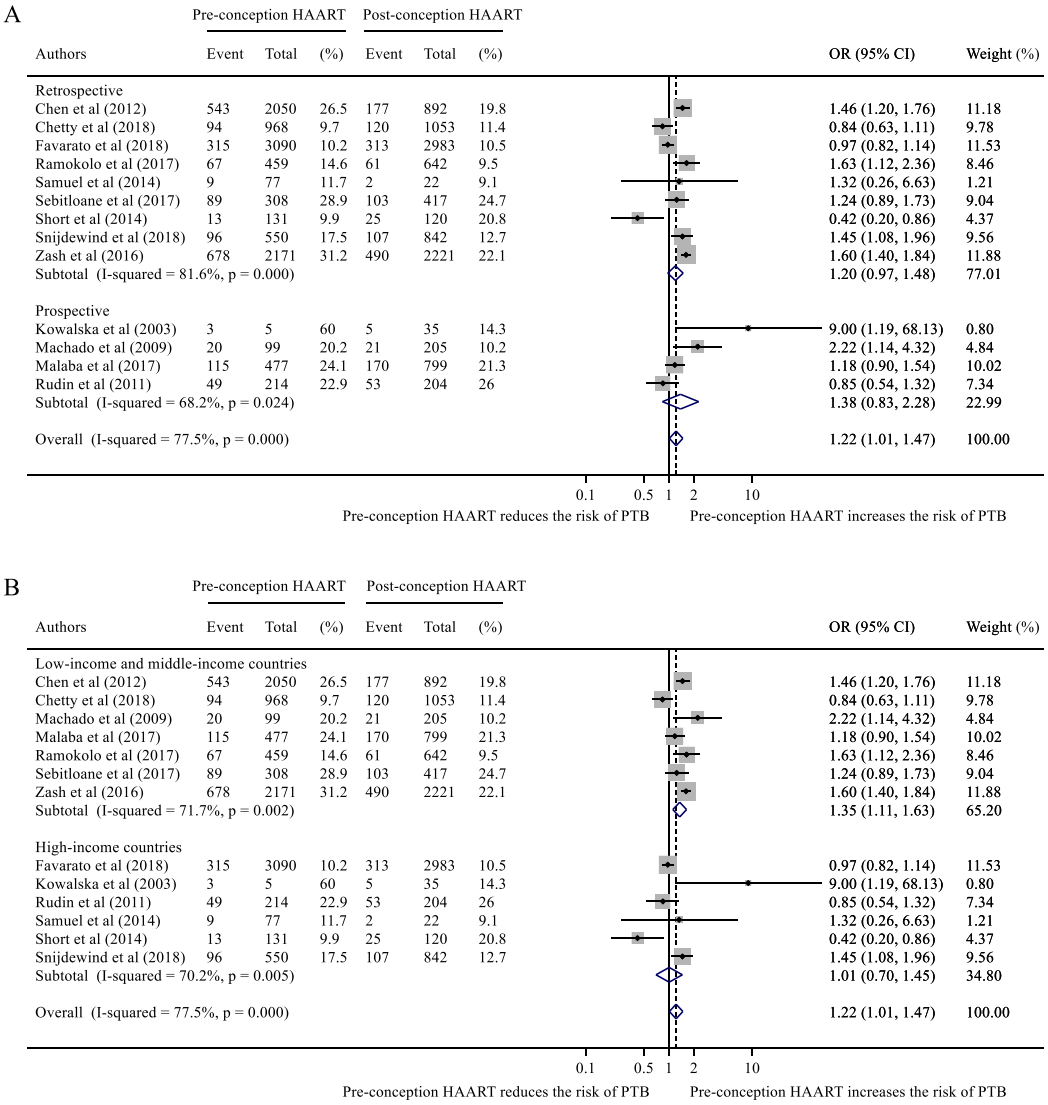


Figure 3.52. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth

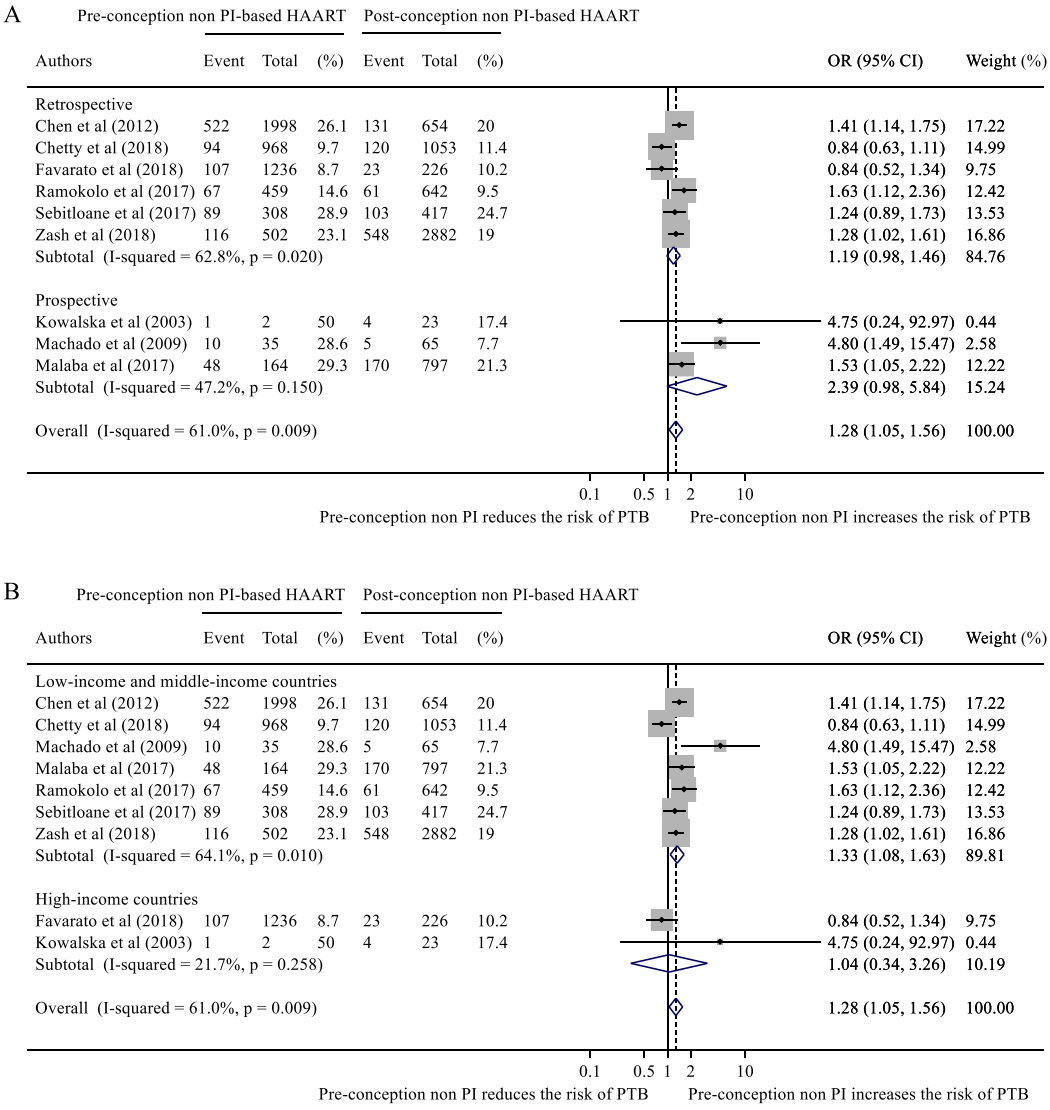


Figure 3.53. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated non PI-based HAART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

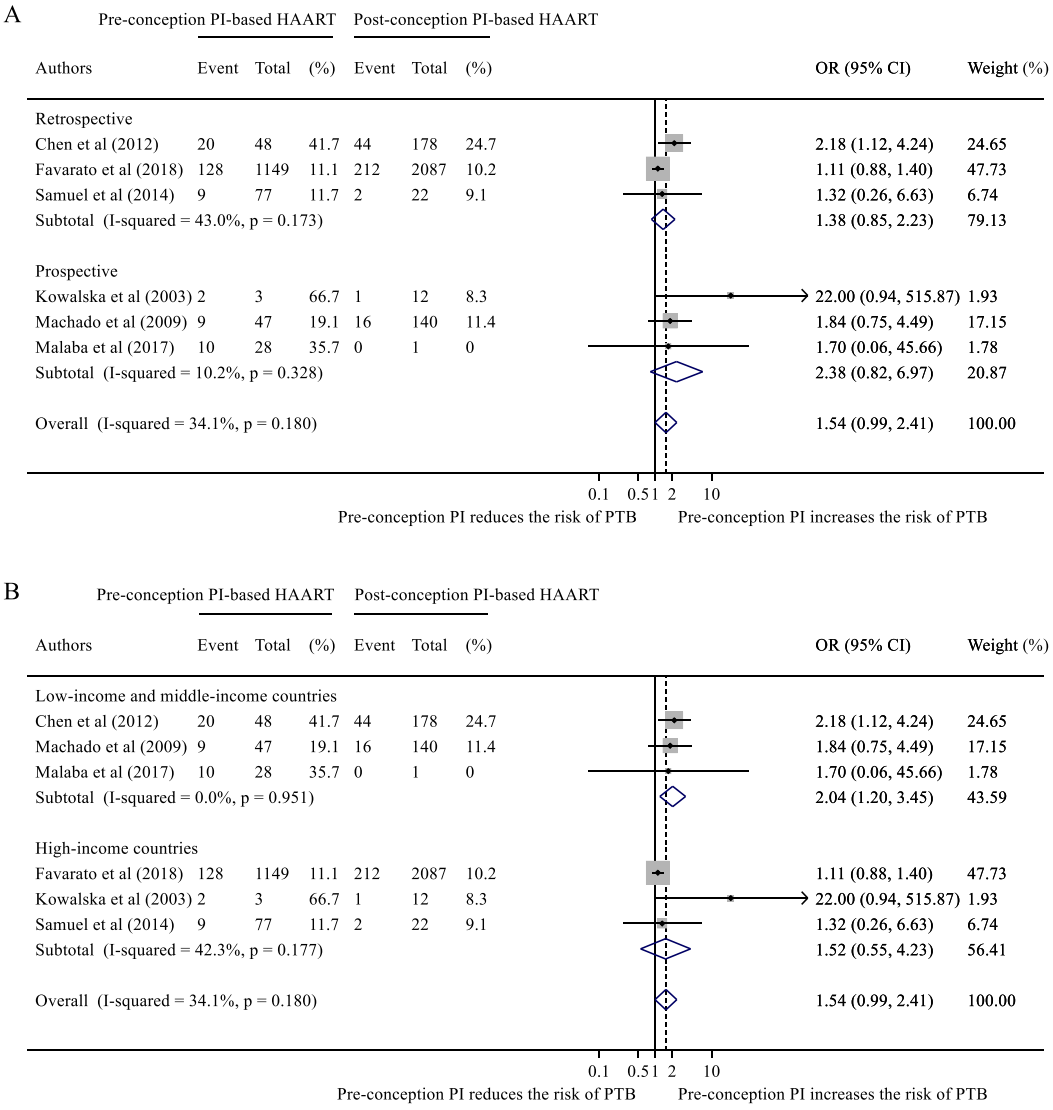


Figure 3.54. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated PI-based HAART pre-conception versus post-conception using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

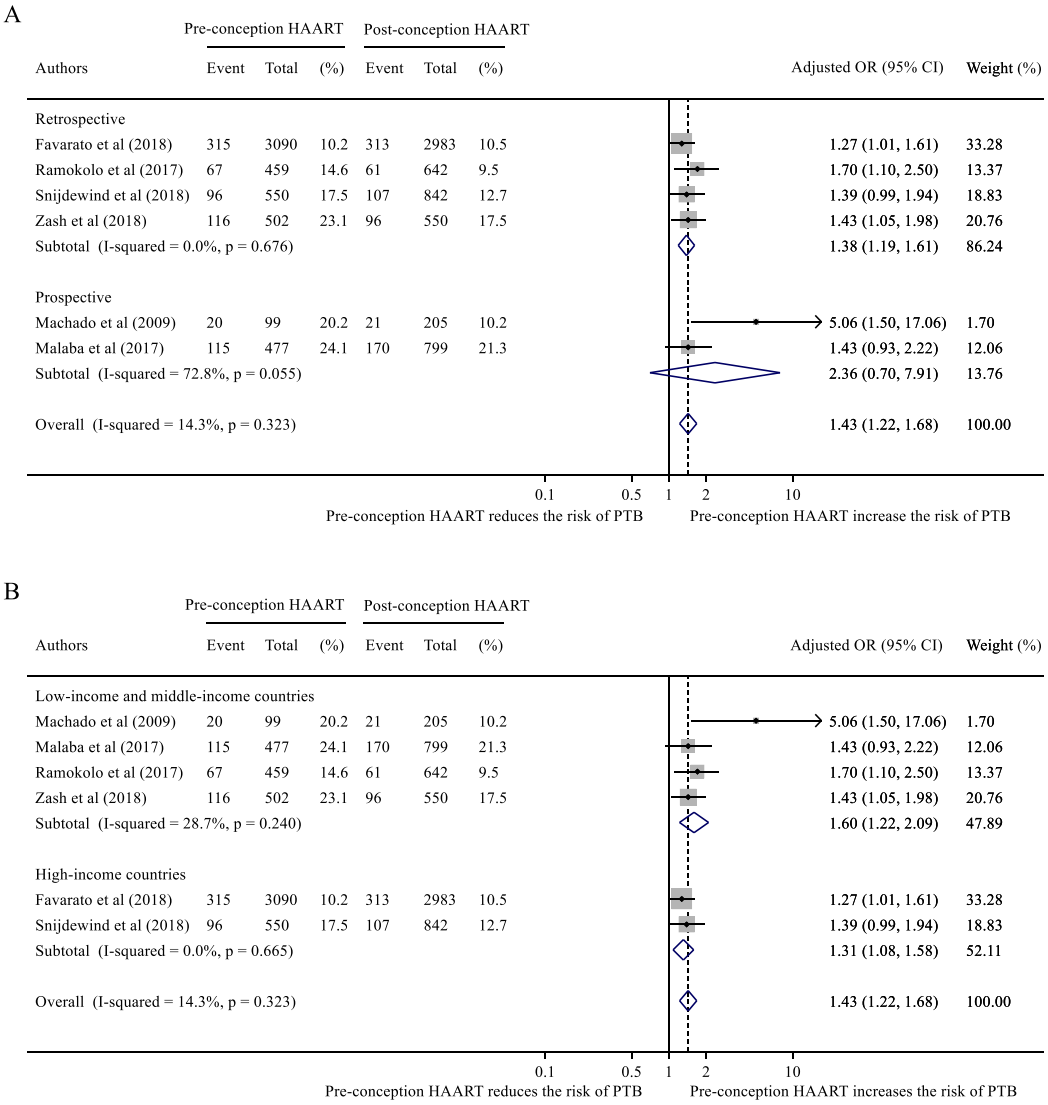


Figure 3.55. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using adjusted effect estimates, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

First trimester versus after first trimester

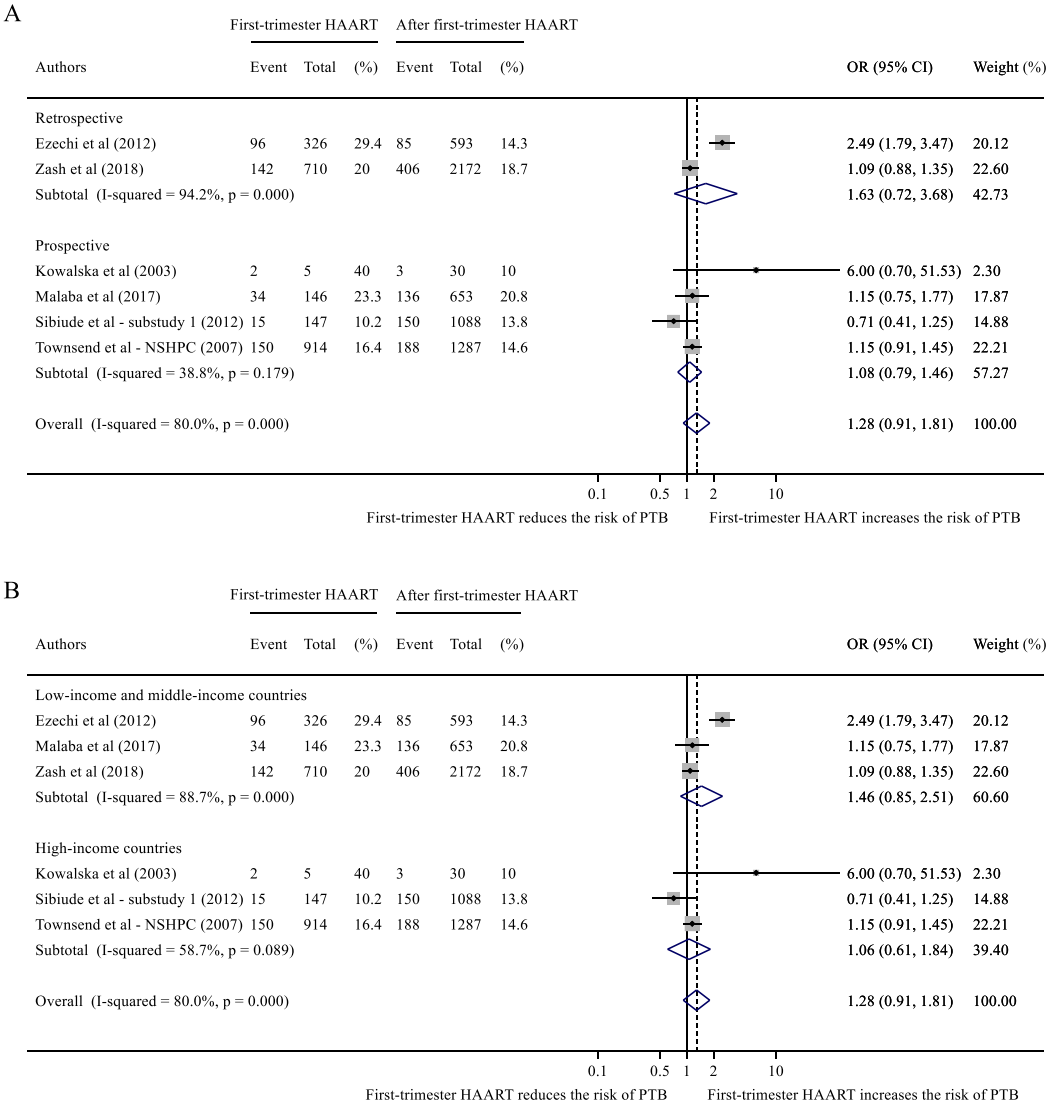


Figure 3.56. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated HAART in the first-trimester versus after first-trimester using unadjusted data, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

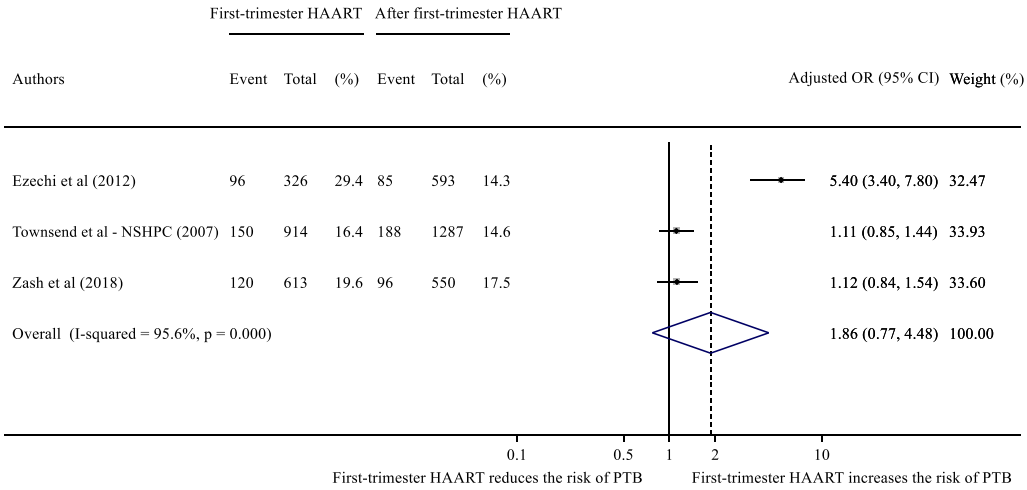


Figure 3.57. Forest plots of risk of preterm birth in HIV-positive pregnant women who initiated HAART in the first-trimester versus after first-trimester using adjusted effect estimates. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; PTB, preterm birth.

Low birth weight

Pre-conception versus post-conception

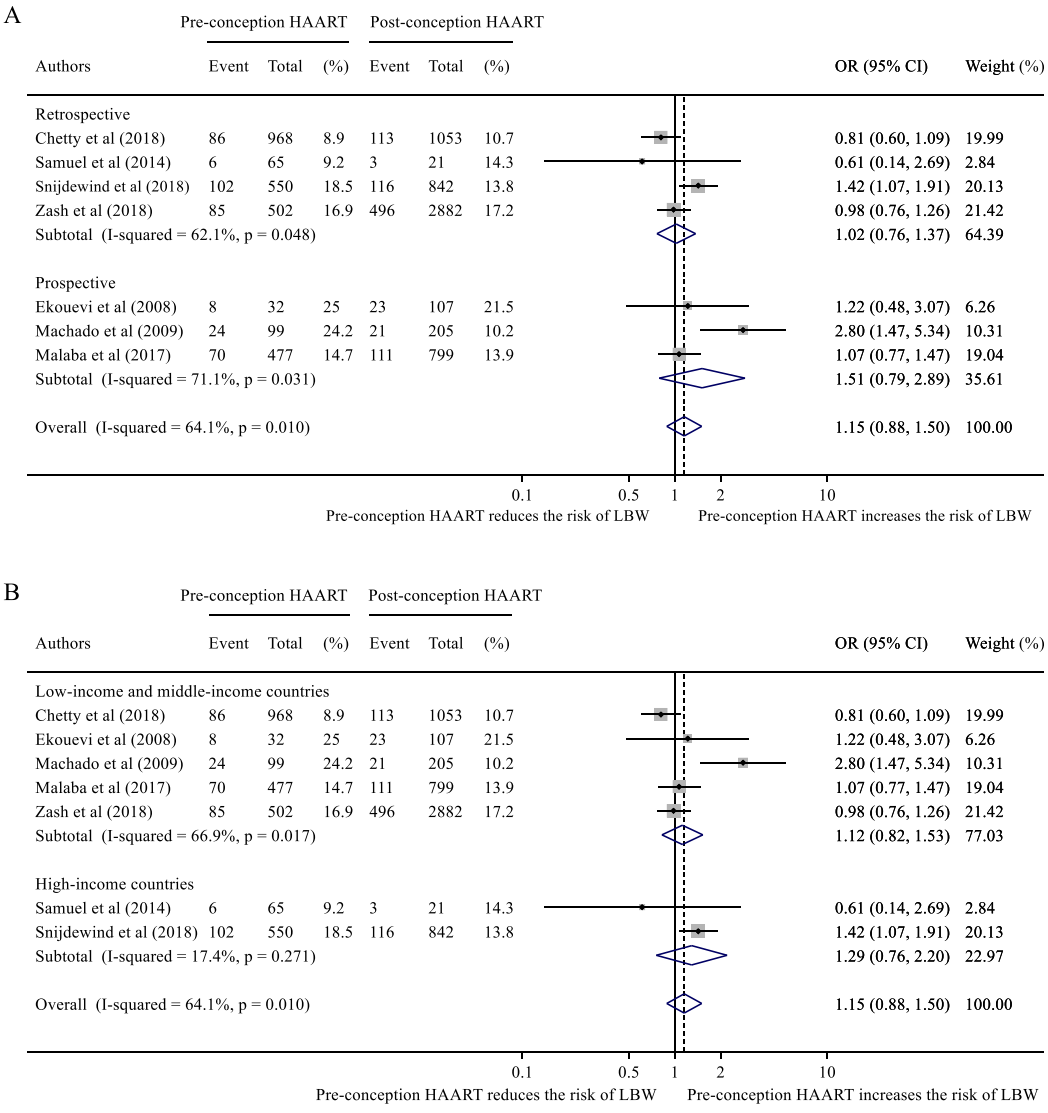


Figure 3.58. Forest plots of risk of low birth weight in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted dara, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

First trimester versus after first trimester

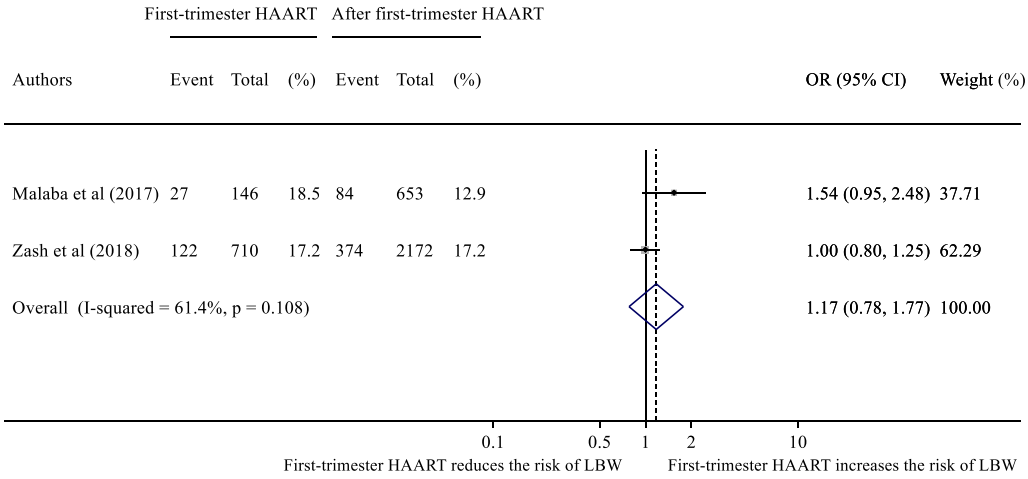


Figure 3.59. Forest plot of risk of low birth weight in HIV-positive pregnant women who initiated HAART in the first-trimester versus after first-trimester using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; OR, odds ratio.

Small for gestational age

Pre-conception versus post-conception

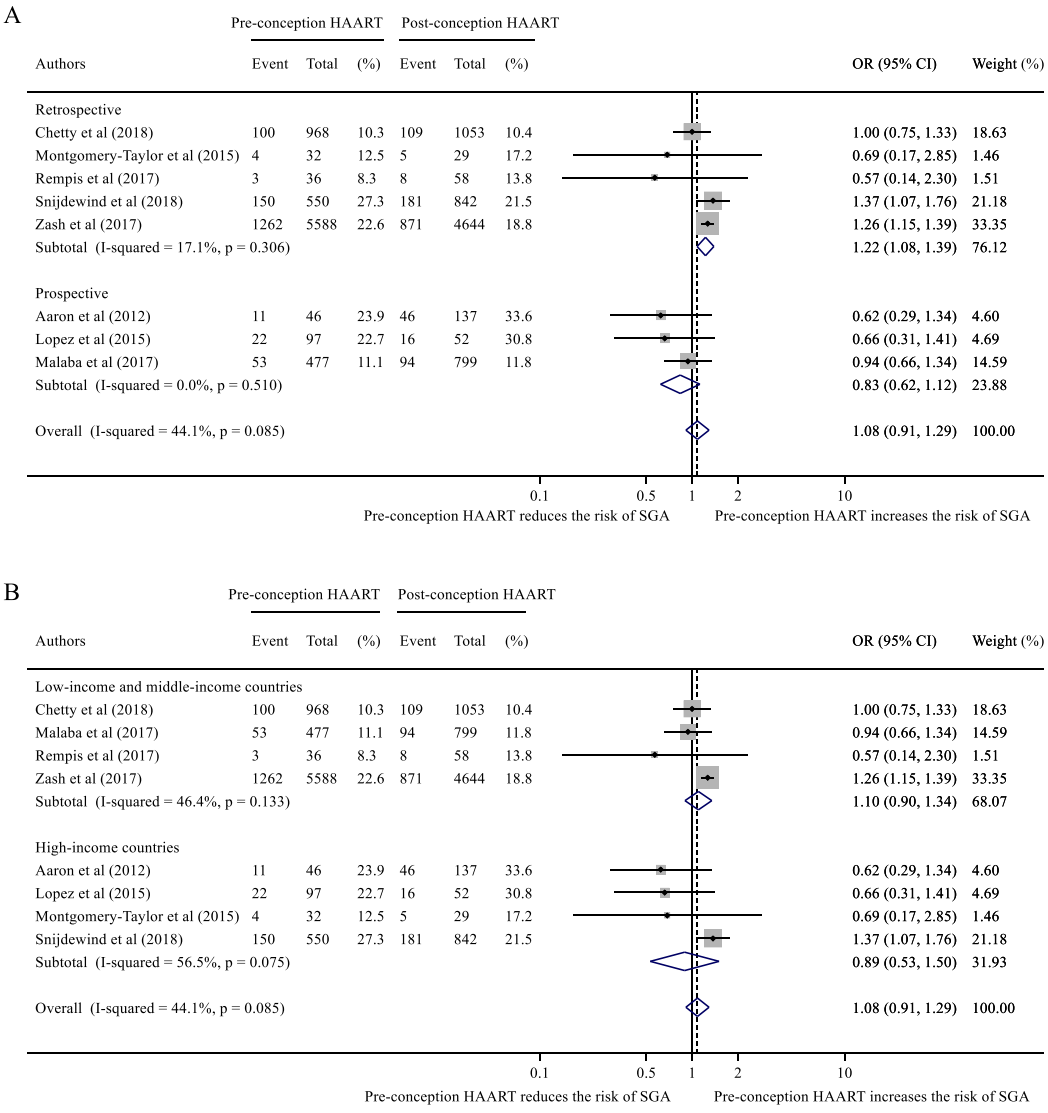


Figure 3.60. Forest plots of risk of small for gestational age in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted dara, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

First trimester versus after first trimester

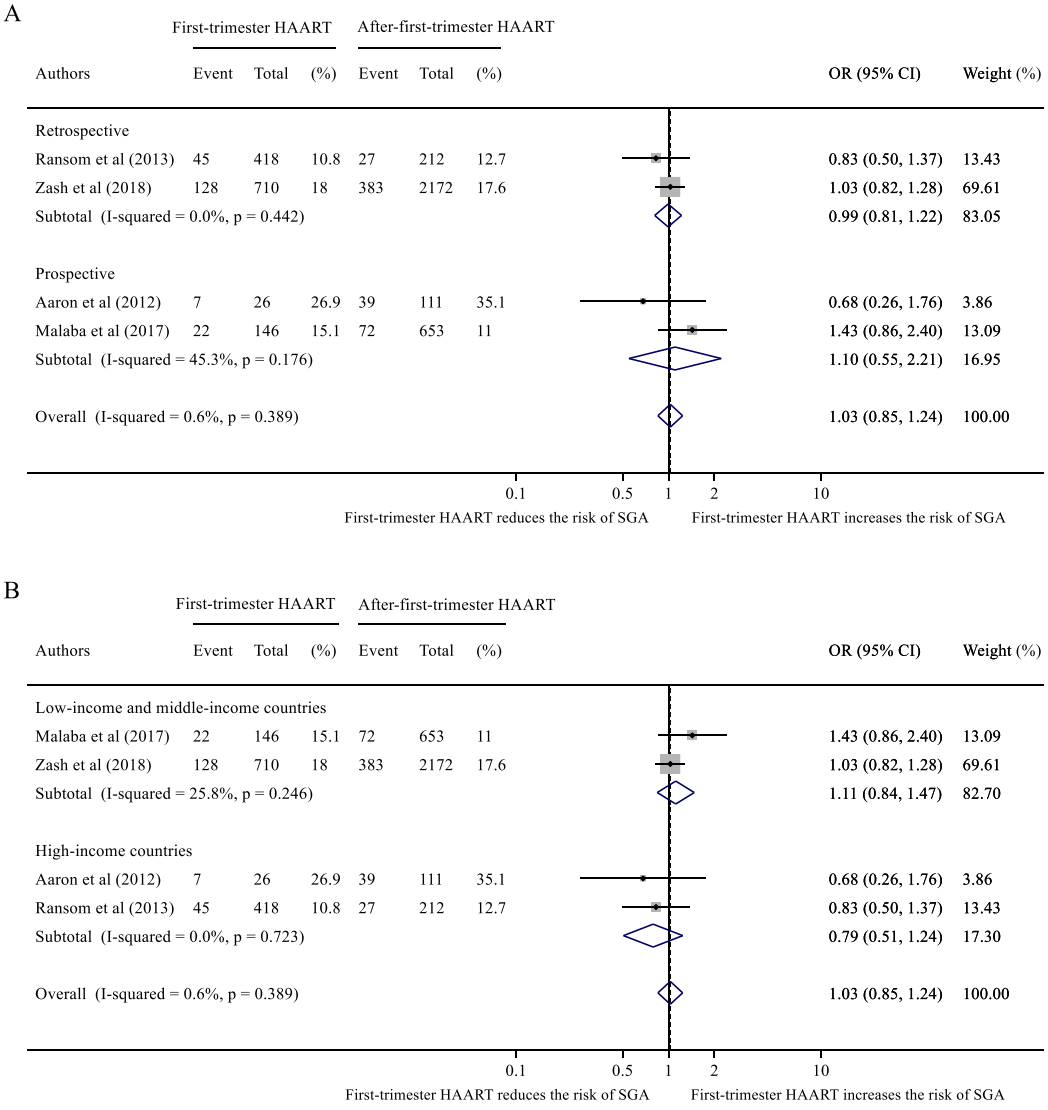


Figure 3.61. Forest plots of risk of small for gestational age in HIV-positive pregnant women who initiated HAART in the first-trimester versus after first-trimester using unadjusted dara, by cohort design (A) and country-income status (B). Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; SGA, small for gestational age.

Very small for gestational age

Pre-conception versus post-conception

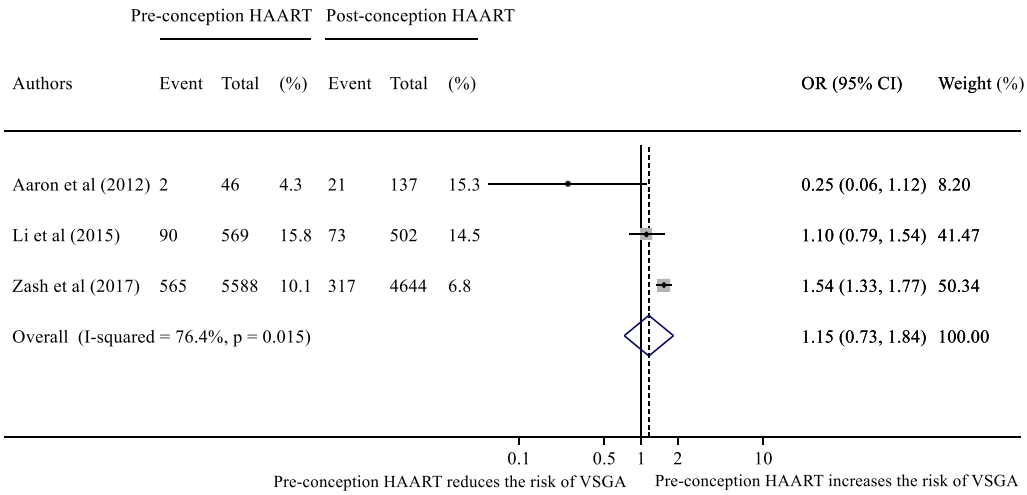


Figure 3.62. Forest plot of risk of very small for gestational age in HIV-positive pregnant women who initiated HAART pre-conception versus post-conception using unadjusted data. Area of boxes indicates the weight given to the individual studies. The width of the line indicates the 95% CIs of the effect estimate of individual studies. The diamond indicates the overall pooled effect estimate. The width of the diamond indicates the 95% CIs for the overall pooled effect estimate. Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OR, odds ratio; VSGA, very small for gestational age.

Table 3.10. Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes using unadjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Pre-conception versus post-conception initiation of ART	PTB	14	1.30 (1.09, 1.54)	84.7	10	1.31 (1.08, 1.58)	87.9	4	1.25 (0.86, 1.82)	52.9	7	1.41 (1.14, 1.75)	85.1	7	1.14 (0.86, 1.51)	79.2
	VPTB	4	1.32 (1.01, 1.73)	30.2							2	1.00 (0.68, 1.47)	0	2	1.49 (1.19, 1.85)	0
	LBW	8	1.17 (0.87, 1.59)	72.5	5	0.98 (0.69, 1.38)	68.1	3	1.64 (0.88, 3.05)	77	5	1.22 (0.88, 1.70)	74.8	3	0.54 (0.12, 2.46)	75.2
	SGA	8	1.08 (0.90, 1.28)	46.3	5	1.20 (1.04, 1.39)	27	3	0.83 (0.62, 1.12)	0	4	1.09 (0.89, 1.34)	51	4	0.89 (0.53, 1.50)	56.5
	VSGA	4	1.19 (0.78, 1.79)	75.4	2	0.86 (0.23, 3.23)	84.2	2	0.74 (0.12, 4.53)	83	2	1.55 (1.37, 1.76)	0	2	0.34 (0.14, 0.80)	0
	Stillbirth	2	1.38 (0.49, 3.85)	94.1												
	MTCT	2	0.20 (0.05, 0.83)	23.4												
Pre-conception versus post-conception initiation of non HAART	PTB	2	0.49 (0.09, 2.70)	0												
Pre-conception versus post-conception initiation of HAART	PTB	13	1.22 (1.01, 1.47)	77.5	9	1.20 (0.97, 1.48)	81.6	4	1.38 (0.83, 2.28)	68.2	7	1.35 (1.11, 1.63)	71.7	6	1.01 (0.70, 1.45)	70.2
	VPTB	3	1.23 (0.76, 1.97)	44.9												
	LBW	7	1.15 (0.88, 1.50)	64.1	4	1.02 (0.76, 1.37)	62.1	3	1.51 (0.79, 2.89)	71.1	5	1.12 (0.82, 1.53)	66.9	2	1.29 (0.76, 2.20)	17.4
	VLBW	3	1.13 (0.68, 1.88)	48.5												
	SGA	8	1.08 (0.91, 1.29)	44.1	5	1.22 (1.08, 1.39)	17.1	3	0.83 (0.62, 1.12)	0	4	1.10 (0.90, 1.34)	46.4	4	0.89 (0.53, 1.50)	56.5
	VSGA	3	1.15 (0.73, 1.84)	76.4												
	NND	1	1.27 (0.92, 1.77)	–												

Table 3.10. Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Pre-conception versus post-conception initiation of non PI-based HAART	PTB	9	1.28 (1.05, 1.56)	61	6	1.19 (0.98, 1.46)	62.8	3	2.39 (0.98, 5.84)	47.2	7	1.33 (1.08, 1.63)	64.1	2	1.04 (0.34, 3.26)	21.7
Pre-conception versus post-conception initiation of PI-based HAART	PTB	6	1.54 (0.99, 2.41)	34.1	3	1.38 (0.85, 2.23)	43	3	2.38 (0.82, 6.97)	10.2	3	2.04 (1.20, 3.45)	0	3	1.52 (0.55, 4.23)	42.3
First trimester versus after first trimester initiation of ART	PTB	10	1.13 (0.88, 1.44)	70.4	5	1.14 (0.75, 1.71)	85.1	5	1.10 (0.91, 1.32)	0	4	1.26 (0.77, 2.03)	86.5	5	1.04 (0.83, 1.30)	31.2
	VPTB	3	1.16 (0.85, 1.58)	8.6												
	LBW	4	1.09 (0.73, 1.61)	44.7	2	0.74 (0.31, 1.81)	56	2	1.51 (0.97, 2.34)	0						
	VLBW	3	1.07 (0.73, 1.56)	0												
	SGA	5	1.04 (0.87, 1.24)	0	3	1.01 (0.84, 1.22)	0	2	1.10 (0.55, 2.21)	45.3	3	1.09 (0.90, 1.31)	0	2	0.79 (0.51, 1.24)	0
	MTCT	1	0.38 (0.12, 1.23)	–												

Table 3.10. Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes using unadjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
First trimester versus after first trimester initiation of HAART	PTB	6	1.28 (0.91, 1.81)	80	2	1.63 (0.72, 3.68)	94.2	4	1.08 (0.79, 1.46)	38.8	3	1.46 (0.85, 2.51)	88.7	3	1.06 (0.61, 1.84)	58.7
	sPTB	1	2.49 (1.79, 3.47)	–												
	VPTB	2	1.34 (0.63, 2.82)	54.2												
	LBW	2	1.17 (0.78, 1.77)	61.4												
	VLBW	2	1.07 (0.72, 1.58)	0												
	SGA	4	1.03 (0.85, 1.24)	0.6	2	0.99 (0.81, 1.22)	0	2	1.10 (0.55, 2.21)	45.3	2	1.11 (0.84, 1.47)	25.8	2	0.79 (0.51, 1.24)	0
	VSGA	2	0.86 (0.61, 1.22)	0												
	Stillbirth	1	0.90 (0.53, 1.53)	–												
	NND	1	1.54 (0.87, 2.74)	–												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; LBW, low birth weight; MTCT, mother-to-child transmission; NND, neonatal death; OR, odds ratio; PI, protease inhibitor; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Table 3.11. Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes using adjusted effect estimates.

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
Pre-conception versus post-conception initiation of ART	PTB	7	1.37 (1.23, 1.54)	4.7	5	1.35 (1.21, 1.51)	0	2	2.36 (0.70, 7.91)	72.8	4	1.60 (1.22, 2.09)	28.7	3	1.31 (1.15, 1.48)	0
Pre-conception versus post-conception initiation of HAART	PTB	6	1.43 (1.22, 1.68)	14.3	4	1.38 (1.19, 1.61)	0	2	2.36 (0.70, 7.91)	72.8	4	1.60 (1.22, 2.09)	28.7	2	1.31 (1.08, 1.58)	0
	VPTB	2	1.28 (0.92, 1.77)	0												
	LBW	5	1.32 (0.95, 1.83)	64.3	3	1.11 (0.89, 1.38)	9.2	2	2.15 (0.85, 5.44)	76.1						
	VLBW	2	1.01 (0.62, 1.65)	0												
	SGA	5	1.27 (1.14, 1.42)	15.5												
	VSGA	2	0.93 (0.25, 3.47)	77.2												
	Stillbirth	1	1.34 (0.64, 2.79)	–												
	NND	1	1.26 (0.89, 1.78)	–												
First trimester versus after first trimester initiation of ART	PTB	4	1.52 (0.73, 3.17)	94												
	SGA	2	1.06 (0.81, 1.40)	0												

Table 3.11. Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes using adjusted effect estimates (*continued from previous page*).

ART comparisons	Perinatal outcomes	Overall meta-analysis			Sub-group analysis by cohort design						Sub-group analysis by country-income status					
					Retrospective			Prospective			Low and middle-income			High-income		
		N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)	N	OR (95% CI)	I^2 (%)
First trimester versus after first trimester initiation of HAART	PTB	3	1.86 (0.77, 4.48)	95.6												
	sPTB	1	5.40 (3.40, 7.80)	–												
	VPTB	1	1.24 (0.69, 2.28)	–												
	LBW	1	1.02 (0.75, 1.42)	–												
	VLBW	1	0.98 (0.55, 1.76)	–												
	VSGA	1	0.71 (0.45, 1.14)	–												
	Stillbirth	1	0.86 (0.40, 1.83)	–												
	NND	1	1.76 (0.75, 4.27)	–												

I^2 indicates the I^2 values for heterogeneity: <25% none, 25-49% low, 50-74% moderate, ≥75% high heterogeneity; N indicates number of cohorts included in a meta-analysis.
Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HAART, highly active antiretroviral therapy; LBW, low birth weight; NND, neonatal death; OR, odds ratio; PTB, preterm birth; SGA, small for gestational age; sPTB, spontaneous PTB; VLBW, very LBW; VPTB, very PTB; VSGA, very SGA.

Summary of meta-analysis results for the effect of timing of ART initiation on perinatal outcomes

Preterm birth (PTB)

Pre-conception versus post-conception

The overall meta-analysis of unadjusted effect estimates including 14 cohorts and 41,092 women, showed that the odds of having a preterm baby in women initiating ART pre-conception were 30% higher than those initiating post-conception (Table 3.10). In sub-group analyses, a similar finding was observed in retrospective cohorts (but not prospective), and in LMIC but not high-income country. However, the I^2 values suggested a high degree of heterogeneity in most of these analyses (Table 3.10).

In sensitivity analyses according to ART complexity, only two cohorts were available for the analysis of women receiving non HAART, suggesting no association between pre-conception initiation of non HAART and PTB (Table 3.10). However, for the analysis of women receiving HAART, 13 cohorts were available, which showed a 22% increase in the odds of having a preterm baby in women initiating HAART pre-conception compared with those initiating post-conception (Table 3.10). Among women on HAART, sensitivity analyses were conducted according to ART class, which showed that both PI and non PI were associated with an increased risk of SGA. Women receiving PI (OR = 1.54) showed a 26% higher OR than those receiving non PI-based HAART (OR = 1.28), which reached borderline statistical significance (Table 3.10).

The overall meta-analysis of adjusted effect estimates, including seven cohorts and 23,533 women, showed a 37% increase in the odds of having a preterm baby in women starting ART pre-conception compared with those starting post-conception (Table 3.11). The finding persisted across country-income status, and in the sub-group analysis of retrospective cohorts (but not prospective). All these findings persisted in sensitivity analyses limited to women on HAART (Table 3.11).

First trimester versus after first trimester

The overall meta-analysis of unadjusted effect estimates, including 10 cohorts and 14,461 women, showed no difference in PTB risk between first trimester and after first trimester initiation of ART (Table 3.10). The finding was consistently observed across cohort design and country-income status, and in the sensitivity analyses limited to women on HAART (Table 3.10).

Four cohorts were available for the meta-analysis of adjusted effect estimates, which showed no association between first trimester initiation of ART and PTB. The finding persisted in the sensitivity analysis limited to women on HAART (Table 3.11).

Very preterm birth (VPTB)

Pre-conception versus post-conception

The pooled unadjusted effect estimates, including 4 cohorts and 14,730 women, showed that women starting ART pre-conception were 1.32 times more likely to have a preterm baby than those starting post-conception (Table 3.10). The finding remained in the sub-group analysis of two cohorts in a high-income country, but

not in the other two LMIC cohorts. In a sensitivity analysis restricted to women on HAART, pre-conception initiation was not associated with VPTB (Table 3.10).

Only two cohorts were available for the meta-analysis of adjusted effect estimates, suggesting no association between pre-conception initiation of HAART and an increased risk of VPTB (Table 3.11).

First trimester versus after first trimester

The pooled unadjusted effect estimates of three cohorts and 8,264 women, showed no association between first trimester initiation of ART and VPTB; the finding remained when the analysis was limited to women receiving HAART (Table 3.10).

Low birth weight (LBW)

Pre-conception versus post-conception

The meta-analysis of unadjusted effect estimates, including 8 cohorts and 9,729 women, showed no association between pre-conception initiation of ART and LBW (Table 3.10). The finding was consistently observed across cohort design and country-income status, and in sensitivity analyses restricted to women treated with HAART (Table 3.10).

Pre-conception initiation remained not associated with LBW in the meta-analysis of adjusted effect estimates of five cohorts, in which all women were on HAART (Table 3.11).

First trimester versus after first trimester

Four cohorts were available for the meta-analysis of unadjusted effect estimates, which showed no association between first trimester initiation and LBW (Table 3.10). The finding persisted across cohort design and in a sensitivity analysis restricted to women on HAART (Table 3.10).

Very low birth weight (VLBW)

Pre-conception versus post-conception

Three cohorts, in which all women were on HAART, were included in the meta-analysis of unadjusted effect estimates: these showed no association between pre-conception initiation and VLBW (Table 3.10). The finding remained in the meta-analysis of adjusted effect estimates with two cohorts (Table 3.11).

First trimester versus after first trimester

The pooled unadjusted effect estimates, including three cohorts and 3,800 women, showed no association between first trimester initiation of ART and VLBW. A similar finding was observed in a sensitivity analysis restricted to women receiving HAART (Table 3.10).

Small for gestational age (SGA)

Pre-conception versus post-conception

In the overall meta-analysis of unadjusted effect estimates including 8 cohorts and 15,936 women, pre-conception initiation of ART was not associated with SGA; the finding remained across country-income status (Table 3.10). However, the sub-group analysis of retrospective, but not prospective cohorts, showed that the odds of having an SGA baby in women with pre-conception initiation were 20%

higher than those with post-conception initiation of ART (Table 3.10). All these findings were consistently observed when the analyses were restricted to women on HAART (Table 3.10).

The meta-analysis of adjusted effect estimates including five cohorts in which all women received HAART, showed that women with pre-conception initiation were 1.27 times more likely to have an SGA baby than those with post-conception initiation; no heterogeneity was observed (Table 3.11).

First trimester versus after first trimester

The pooled unadjusted effect estimates, including five cohorts and 6,029 women, showed no association between first trimester initiation of ART and SGA (Table 3.10). The finding persisted across cohort design and country-income status, and in sensitivity analyses restricted to women on HAART (Table 3.10), as well as in the meta-analysis of adjusted effect estimates (Table 3.11). However, few studies were included in these analyses (Tables 3.10 and 3.11).

Very small for gestational age (VSGA)

Pre-conception versus post-conception

The overall meta-analysis of unadjusted effect estimates of four cohorts revealed no association between pre-conception initiation of ART and VSGA; the finding persisted across cohort design (Table 3.10). However, the sub-group analysis of cohorts conducted in LMICs, but not in high-income countries, showed that pre-conception initiation of ART was associated with a 55% increase in the odds of having a VSGA baby (Table 3.10). In a sensitivity analysis restricted to women

receiving HAART, pre-conception initiation remained not associated with VSGA. However, all these results were synthesised from few studies (Table 3.10).

The pooled adjusted effect estimates of two cohorts revealed that there was no association between pre-conception initiation of HAART and VSGA (Table 3.11).

First trimester versus after first trimester

Only two cohorts were available for the meta-analysis of unadjusted effect estimates, which suggested that there was no association between first trimester initiation of HAART and VSGA (Table 3.10).

Stillbirth

Pre-conception versus post-conception

Two cohorts were included the meta-analysis of unadjusted effect estimates, which suggested that there was no association between pre-conception initiation of ART and stillbirth (Table 3.10).

Mother-to-child transmission (MTCT)

Pre-conception versus post-conception

Pre-conception initiation of ART was associated with an 80% reduction in the odds of MTCT of HIV; however, only two cohorts were included in this analysis (Table 3.10).

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Chapter 5: List of appendices

Appendix 5.1 : Maternal characteristics of HIV-positive women according to participation in the SHAPOSSA Study.

Appendix 5.2 : Maternal characteristics according to HIV status stratified by education.

Appendix 5.1

Maternal characteristics of HIV-positive women according to participation in the SHAPOSSA Study.

Table 5.1. Maternal characteristics of HIV-positive women according to participation in the SHAPOSSA Study.

Maternal characteristics	**All HIV+ (N=220) n (%)**	**HIV+ participated in SHAPOSSA**		***P* value[§]**
		Yes (N=122) n (%)	**No (N=98) n (%)**	
Age (years), median (IQR)	32 (28, 37)	32 (27, 36)	33 (28, 38)	0.117
Education (years), median (IQR)	12 (11, 12)	12 (11, 12)	12 (11, 12)	0.235
Single	146 (66.4)	75 (61.5)	71 (72.5)	0.087
Smoking	16 (7.3)	9 (7.4)	7 (7.1)	0.947
Alcohol consumption	22 (10)	13 (10.7)	9 (9.2)	0.718
Illicit drug use	2 (0.9)	2 (1.6)	0	0.504
Socio-economic status				
Low	38 (17.3)	21 (17.2)	17 (17.4)	0.522
Middle	113 (51.4)	59 (48.4)	54 (55.1)	
High	69 (31.4)	42 (34.4)	27 (27.5)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.4 (22.9, 30)	26.7 (23.2, 29.9)	26.1 (22.1, 30.1)	0.443
Nulliparity	24 (11.4)	16 (13.6)	8 (8.7)	0.272
Number of previous miscarriages ≥2	35 (15.9)	21 (17.2)	14 (14.3)	0.555
History of adverse perinatal outcomes	71 (32.3)	35 (28.7)	36 (36.7)	0.205
Gestational age at enrolment (weeks), median (IQR)	12 (10.5, 13)	12 (10, 13)	12 (11, 13)	0.220
Number of antenatal care visits, median (IQR)	4 (2, 5)	5 (4, 5)	5 (4, 5)	0.922
GWG in the second trimester				
Inadequate	91 (42)	53 (43.8)	38 (39.6)	0.349
Adequate	53 (24.4)	25 (20.7)	28 (29.2)	
Excessive	73 (33.6)	43 (35.5)	30 (31.2)	

Table 5.1. Maternal characteristics of HIV-positive women according to participation in the SHAPOSSA Study (*continued from previous page*).

Maternal characteristics	**All HIV+ (N=220) n (%)**	**HIV+ participated in SHAPOSSA**		***P* value[§]**
		Yes (N=122) n (%)	**No (N=98) n (%)**	
GWG in the third trimester				
Inadequate	70 (35.7)	38 (34.6)	32 (37.2)	0.916
Adequate	43 (21.9)	25 (22.7)	18 (20.9)	
Excessive	83 (42.4)	47 (42.7)	36 (41.9)	
Malaria	0	0	0	
Syphilis	1 (0.5)	0	1 (1.0)	0.445
Genital tract/sexually-transmitted infections	5 (2.3)	4 (3.3)	1 (1.0)	0.384
Gestational hypertension	22 (10)	9 (7.4)	13 (13.3)	0.148
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.1 ± 1.6	12.3 ± 1.5	12.8 ± 1.7	0.433
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.8 ± 1.5	11.7 ± 1.4	11.8 ± 1.6	0.733
Haemoglobin level in the third trimester (g/dL), mean ± SD	11.3 ± 1.7	11.4 ± 1.7	11.2 ± 1.8	0.383
Caesarean section	126 (57.3)	78 (63.9)	48 (49.0)	0.026

[§] *P* value from t-test, Wilcoxon-Mann-Whitney, chi-square, or Fisher's exact test, as appropriate, for comparisons between HIV-positive women participating in the SHAPOSSA Study and those not participating.
Missing data<8%.
Abbreviations: BMI, body mass index; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

Appendix 5.2

Maternal characteristics according to HIV status stratified by education.

Table 5.2. Maternal characteristics according to HIV status stratified by education.

Maternal characteristics	All women (N=596) n (%)	Women with ≤11 years' education			Women with >11 years' education		
		HIV-negative (N=82) n (%)	HIV-positive (N=83) n (%)	*P* value[§]	HIV-negative (N=294) n (%)	HIV-positive (N=137) n (%)	*P* value[§]
Age (years), median (IQR)	31 (26, 35.5)	30 (26, 37)	33 (28, 38)	0.043	30 (25, 34)	32 (28, 36)	0.002
Single	362 (60.7)	45 (54.9)	52 (62.7)	0.311	171 (58.2)	94 (68.6)	0.038
Smoking	38 (6.4)	8 (9.8)	10 (12.1)	0.637	14 (4.8)	6 (4.4)	0.861
Alcohol consumption	49 (8.2)	6 (7.3)	6 (7.2)	0.983	21 (7.1)	16 (11.7)	0.118
Illicit drug use	3 (0.5)	0	1 (1.2)	1.000	1 (0.3)	1 (0.7)	0.535
Socio-economic status							
Low	115 (19.3)	29 (35.4)	20 (24.1)	0.175	48 (16.3)	18 (13.1)	0.203
Middle	262 (44)	36 (43.9)	48 (57.8)		113 (38.5)	65 (47.5)	
High	219 (36.7)	17 (20.7)	15 (18.1)		133 (45.2)	54 (39.4)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.7 (23.2, 30.1)	27.5 (24.5, 30.7)	26.1 (23.0, 30.4)	0.234	26.7 (23.2, 30.0)	26.9 (22.7, 30.0)	0.885

Table 5.2. Maternal characteristics according to HIV status stratified by education (*continued from previous page*).

Maternal characteristics	All women (N=596) n (%)	Women with ≤11 years' education			Women with >11 years' education		
		HIV-negative (N=82) n (%)	HIV-positive (N=83) n (%)	*P* value[§]	HIV-negative (N=294) n (%)	HIV-positive (N=137) n (%)	*P* value[§]
Nulliparity	90 (16.2)	12 (14.8)	6 (7.3)	0.127	54 (20.3)	18 (14.1)	0.133
Number of previous miscarriages ≥2	126 (21.1)	20 (24.4)	8 (9.6)	0.012	71 (24.2)	27 (19.7)	0.306
History of adverse perinatal outcomes	201 (33.7)	25 (30.5)	29 (34.9)	0.542	105 (35.7)	42 (30.7)	0.302
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (11, 13)	0.439	12 (11, 13)	11 (10, 13)	0.046
Number of antenatal care visits, median (IQR)	4 (2, 5)	5 (4, 5)	5 (4, 5)	0.259	5 (4, 5)	5 (4, 5)	0.542
GWG in the second trimester							
Inadequate	210 (35.8)	32 (41)	33 (40.7)	0.319	87 (29.9)	58 (42.6)	0.016
Adequate	130 (22.2)	15 (19.3)	23 (28.4)		62 (21.3)	30 (22.1)	
Excessive	246 (42)	31 (39.7)	25 (30.9)		142 (48.8)	48 (35.3)	
GWG in the third trimester							
Inadequate	164 (30)	27 (35.5)	30 (41.1)	0.719	67 (24.4)	40 (32.5)	0.063
Adequate	109 (20)	14 (18.4)	14 (19.2)		52 (19)	29 (23.6)	
Excessive	273 (50)	35 (46.1)	29 (39.7)		155 (56.6)	54 (43.9)	
Malaria	0	0	0		0	0	

Table 5.2. Maternal characteristics according to HIV status stratified by education (*continued from previous page*).

Maternal characteristics	All women (N=596) n (%)	Women with ≤11 years' education			Women with >11 years' education		
		HIV-negative (N=82) n (%)	HIV-positive (N=83) n (%)	*P* value[§]	HIV-negative (N=294) n (%)	HIV-positive (N=137) n (%)	*P* value[§]
Syphilis	1 (0.2)	0	1 (1.2)	1.000	0	0	
Genital tract/sexually-transmitted infections	8 (1.3)	0	2 (2.4)	0.497	3 (1.0)	3 (2.2)	0.388
Gestational hypertension	60 (10)	8 (9.8)	10 (12.1)	0.637	30 (10.2)	12 (8.8)	0.638
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.2 ± 1.7	12.1 ± 1.5	12.0 ± 1.7	0.594	12.3 ± 1.8	12.2 ± 1.5	0.583
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.9 ± 1.5	11.9 ± 1.7	11.8 ± 1.6	0.638	12.1 ± 1.5	11.8 ± 1.4	0.026
Haemoglobin level in the third trimester (g/dL), mean ± SD	11.6 ± 1.7	11.6 ± 1.7	11.2 ± 1.6	0.129	11.9 ± 1.6	11.3 ± 1.7	0.001
Caesarean section	338 (56.7)	53 (64.6)	46 (55.4)	0.227	159 (54.1)	80 (58.4)	0.402

[§] *P* value from t-test, Wilcoxon-Mann-Whitney, chi-square, or Fisher's exact test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
Missing data<8%.
Abbreviations: BMI, body mass index; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

Table 5.3. Maternal HIV-related characteristics among women with ART information, according to education.

Maternal HIV-related characteristics	**HIV-positive women with ART information (N=106)**		***P* value[§]**
	≤11 years' education (N=35) n (%)	**>11 year' education (N=71) n (%)**	
Clinical stage of HIV			
Stage 1	35 (100)	65 (94.2)	0.400
Stage 2	0	2 (2.9)	
Stage 3	0	2 (2.9)	
Stage 4	0	0	
Antenatal CD4 count (cells/mm^3), median (IQR)	446.5 (309.5, 550.5)	460.3 (349.0, 686.0)	0.438

[§] *P* value from Wilcoxon-Mann-Whitney or Fisher's exact test, as appropriate, for comparisons between HIV-positive women with ≤11 and >11 years' education.
Missing data: <3%.
Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

Chapter 6: List of appendices

Appendix 6.1 : Maternal characteristics in single versus married/cohabiting women.

Appendix 6.2 : Maternal HIV/ART, nutrition and perinatal outcomes.

Appendix 6.1

Maternal characteristics in single versus married/cohabiting women.

Table 6.1. Maternal characteristics according to HIV status in single versus married/cohabiting women.

Maternal characteristics	**All women (N=578) n (%)**	**Single (N=352)**			**Married/cohabiting (N=226)**		
		HIV-negative (N=209) n (%)	**HIV-positive (N=143) n (%)**	***P* value[§]**	**HIV-negative (N=155) n (%)**	**HIV-positive (N=71) n (%)**	***P* value[§]**
Age (years), median (IQR)	31 (26, 36)	28 (25, 33)	33 (27, 38)	<0.001	31 (28, 36)	32 (28, 37)	0.435
Education (years), median (IQR)	12 (11, 12)	12 (12, 12)	12 (11, 12)	0.016	12 (11, 12)	12 (11, 12)	0.533
Smoking	38 (6.6)	16 (7.7)	13 (9.1)	0.630	6 (3.9)	3 (4.2)	1.000
Alcohol consumption	46 (8)	19 (9.1)	14 (9.8)	0.825	7 (4.5)	6 (8.5)	0.236
Illicit drug use	3 (0.5)	1 (0.5)	2 (1.4)	0.569	0	0	–
Socio-economic status							
Low	107 (18.5)	45 (21.5)	25 (17.5)	0.198	27 (17.4)	10 (14.1)	0.136
Middle	256 (44.3)	85 (40.7)	72 (50.3)		61 (39.4)	38 (53.5)	
High	215 (37.2)	79 (37.8)	46 (32.2)		67 (43.2)	23 (32.4)	
Pre-pregnancy BMI (kg/m^2), median (IQR)	26.6 (23.2, 30)	26.6 (23.3, 29.7)	26.1 (22.3, 29.6)	0.317	27.1 (23.8, 30.8)	27.6 (24.1, 30.8)	0.761

Table 6.1. Maternal characteristics according to HIV status in single versus married/cohabiting women (*continued from previous page*).

Maternal characteristics	All women (N=578) n (%)	Single (N=352)			Married/cohabiting (N=226)		
		HIV-negative (N=209) n (%)	HIV-positive (N=143) n (%)	*P* value[§]	HIV-negative (N=155) n (%)	HIV-positive (N=71) n (%)	*P* value[§]
Nulliparity	85 (15.8)	45 (24.2)	15 (11.1)	0.003	18 (12.1)	7 (10.1)	0.677
Number of previous miscarriages ≥2	120 (20.8)	44 (21.1)	20 (14)	0.091	43 (27.7)	13 (18.3)	0.127
History of preterm birth	107 (19.9)	33 (17.7)	29 (21.5)	0.402	33 (22.2)	12 (17.4)	0.420
History of termination of pregnancy	34 (5.9)	11 (5.3)	13 (9.1)	0.162	7 (4.5)	3 (4.2)	1.000
Gestational age at enrolment (weeks), median (IQR)	12 (11, 13)	12 (11, 13)	12 (11, 13)	0.798	12 (10, 13)	11 (10, 12)	0.013
Number of antenatal care visits, median (IQR)	5 (4, 5)	5 (4, 5)	5 (4, 5)	0.020	5 (4, 5)	5 (4, 5)	0.525
GWG in the second trimester							
Inadequate	207 (36.3)	72 (34.6)	61 (43)	0.041	46 (30.7)	28 (40)	0.225
Adequate	126 (22.1)	44 (21.2)	36 (25.3)		30 (20)	16 (22.9)	
Excessive	237 (41.6)	92 (44.2)	45 (31.7)		74 (49.3)	26 (37.1)	
GWG in the third trimester							
Inadequate	162 (30.2)	59 (28.9)	46 (36.8)	0.271	33 (23.7)	24 (34.8)	0.067
Adequate	108 (20.1)	40 (19.6)	25 (20)		26 (18.7)	17 (24.6)	
Excessive	267 (49.7)	105 (51.5)	54 (43.2)		80 (57.6)	28 (40.6)	

Table 6.1. Maternal characteristics according to HIV status in single versus married/cohabiting women (*continued from previous page*).

Maternal characteristics	All women (N=578) n (%)	Single (N=352)			Married/cohabiting (N=226)		
		HIV-negative (N=209) n (%)	HIV-positive (N=143) n (%)	*P* value[§]	HIV-negative (N=155) n (%)	HIV-positive (N=71) n (%)	*P* value[§]
Malaria	0	0	0	–	0	0	–
Syphilis	1 (0.2)	0	1 (0.7)	0.406	0	0	–
Genital tract/sexually-transmitted infections	8 (1.4)	1 (0.5)	5 (3.5)	0.043	2 (1.3)	0	1.000
Gestational hypertension	54 (9.3)	17 (8.1)	15 (10.5)	0.450	17 (11)	5 (7)	0.355
Haemoglobin level in the first trimester (g/dL), mean ± SD	12.2 ± 1.7	12.3 ± 1.7	12.1 ± 1.5	0.189	12.2 ± 1.8	12.3 ± 1.7	0.887
Haemoglobin level in the second trimester (g/dL), mean ± SD	11.9 ± 1.5	11.9 ± 1.5	11.8 ± 1.4	0.28	12.2 ± 1.6	12.0 ± 1.6	0.728
Haemoglobin level in the third trimester (g/dL), mean ± SD	11.6 ± 1.7	11.7 ± 1.6	11.2 ± 1.7	0.006	12.0 ± 1.6	11.4 ± 1.7	0.015
Caesarean section	333 (57.6)	117 (56)	89 (62.2)	0.242	90 (58.1)	37 (52.1)	0.403

[§] *P* value from t-test, Wilcoxon-Mann-Whitney, chi-square, or Fisher's exact test, as appropriate, for comparisons between HIV-negative and HIV-positive women.
Missing data<8%.
Abbreviations: BMI, body mass index; GWG, gestational weight gain; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

Table 6.2. Maternal HIV-related characteristics among women with ART information in single versus married/cohabiting women.

Maternal HIV-related characteristics	**HIV-positive women with ART information (N=106)**		***P* value[§]**
	Single (N=62) n (%)	**Married/cohabiting (N=44) n (%)**	
Clinical stage of HIV			
Stage 1	59 (95.2)	40 (97.6)	0.776
Stage 2	2 (3.2)	0	
Stage 3	1 (1.6)	1 (2.4)	
Stage 4	0	0	
Antenatal CD4 count (cells/mm^3), median (IQR)	420.5 (294, 535)	472 (385, 703)	0.053

[§] *P* value from Wilcoxon-Mann-Whitney or Fisher's exact test, as appropriate, for comparisons between single and married/ cohabiting HIV-positive women.
Missing data: <3%.
Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

Appendix 6.2

Maternal HIV/ART, nutrition and perinatal outcomes.

Table 6.3. Pre-pregnancy body mass index category in all women, HIV negative and HIV-positive women.

Pre-pregnancy body mass index	All women (N=578) n (%)	HIV-negative (N=364) n (%)	HIV-positive (N=214) n (%)	*P* value[§]
Underweight (<18.5 kg/m^2)	10 (1.7)	8 (2.2)	2 (0.9)	0.370
Normal weight (18.5–24.99 kg/m^2)	204 (35.3)	120 (32)	84 (39.3)	
Overweight (25–29.9 kg/m^2)	219 (37.9)	143 (39.3)	76 (35.5)	
Obese (≥30 kg/m^2)	145 (25.1)	93 (25.5)	52 (24.3)	

[§] *P* value from Fisher's exact test for comparison between HIV-negative and HIV-positive women.
Abbreviation: HIV, human immunodeficiency virus.

Table 6.4. Adjusted association between maternal HIV status and pre-pregnancy body mass index.

	Pre-pregnancy body mass index Adjusted β (95% CI)[§]
HIV positive	-0.39 (-1.15, 0.38)
Single	-0.70 (-1.44, 0.05)
Alcohol consumption	1.56 (0.17, 2.96)
Low socio-economic status (Ref: high socio-economic status)	-0.90 (-1.70, -0.09)

[§] Adjusted for all variables in the table, maternal age, education, smoking, parity, history of miscarriages and history of adverse perinatal outcomes.
Abbreviations: β, beta coefficient; CI, confidence interval; HIV, human immunodeficiency virus.

Table 6.5. Maternal factors associated with pre-pregnancy body mass index in HIV-positive women.

Maternal factors	Pre-pregnancy body mass index Adjusted β (95% CI)[§]
Single	-0.90 (-1.69, -0.11)
Alcohol consumption	3.71 (1.55, 5.88)
Low socio-economic status (Ref: high socio-economic status)	-1.77 (-3.64, 0.10)
Nulliparity	-2.08 (-4.10, -0.06)

[§] Adjusted for all variables in the table, maternal age, education, smoking, history of miscarriages and history of adverse perinatal outcomes.
Abbreviations: β, beta coefficient; CI, confidence interval; HIV, human immunodeficiency virus.

Table 6.6. Adjusted associations between maternal HIV status and gestational weight gain in the second and third trimesters.

	Rate of gestational weight gain (kg/week)	
	Second trimester Adjusted β (95% CI)[§]	Third trimester Adjusted β (95% CI)[§]
HIV positive	-0.05 (-0.09, -0.01)	-0.05 (-0.10, 0.00)
Maternal age	0.00 (-0.00, 0.00)	-0.01 (-0.01, -0.003)
Alcohol consumption	-0.09 (-0.17, -0.02)	-0.00 (-0.10, 0.09)
Low socio-economic status (Ref: high socio-economic status)	-0.06 (-0.11, -0.01)	-0.01 (-0.08, 0.06)
Pre-pregnancy BMI	-0.01 (-0.01, -0.01)	-0.00 (-0.01, 0.00)

[§] Adjusted for all variables in the table, education, marital status, smoking, parity, history of miscarriages and history of adverse perinatal outcomes.
Abbreviations: β, beta coefficient; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus.

Table 6.7. Maternal factors associated with gestational weight gain in the second and third trimesters in HIV-positive women.

Maternal factors	Rate of gestational weight gain (kg/week)	
	Second trimester Adjusted β (95% CI)[§]	Third trimester Adjusted β (95% CI)[§]
Alcohol consumption	-0.13 (-0.25, -0.02)	-0.03 (-0.17, 0.10)
Pre-pregnancy BMI	-0.01 (-0.02, -0.00)	-0.00 (-0.01, 0.01)

[§] Adjusted for all variables in the table, maternal age, education, marital status, smoking, socio-economic status, parity, history of miscarriages and history of adverse perinatal outcomes.
Abbreviations: β, beta coefficient; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus.

Chapter 7: List of appendices

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Appendix 7.2 : Fetal biometric parameters compared to the INTERGROWTH-21st Fetal Growth Standards.

Appendix 7.3 : Maternal HIV status and newborn anthropometry.

Appendix 7.1

Multilevel models

Table 7.1. Details of multilevel models.

Group of women	Fetal biometry	Functional form	Powers	Deviance
HIV-negative	BPD	Second-order fractional polynomials	2, 2	7 587
	HC	Second-order fractional polynomials	2, 2	11 768
	AC	Second-order fractional polynomials	1, 3	12 655
	FL	Second-order fractional polynomials	0.5, 3	7 197
HIV-positive	BPD, HC, AC, FL	Restricted cubic splines with three-knot points (21, 29 and 37 weeks)	–	–
Pre-conception ART	BPD, HC, AC, FL	Restricted cubic splines with three-knot points (21, 29 and 37 weeks)	–	–
Post-conception ART	BPD	Second-order fractional polynomials	2, 2	1 426
	HC	Second-order fractional polynomials	2, 2	2 076
	AC	Second-order fractional polynomials	0.5, 2	2 306
	FL	Second-order fractional polynomials	0.5, 3	1 268

Abbreviations: AC, abdominal circumference; ART, antiretroviral therapy; BPD, biparietal diameter; FL, femur length; HC, head circumference; HIV, human immunodeficiency virus.

Appendix 7.2

Fetal biometric parameters compared to the INTERGROWTH-21st Fetal Growth Standards

Table 7.2. Fetal BPD by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st standards.

Gestational age (weeks)	HIV-negative (N=389)		HIV-positive (N=223)		INTERGROWTH-21st standards	
	Number of scans	Mean BPD (mm)	Number of scans	Mean BPD (mm)	10th centile (mm)	50th centile (mm)
15	31	31.4	21	31.6	30.2	32.6
16	54	35.6	34	35.2	33.2	35.7
17	108	38.7	65	38.6	36.2	38.8
18	134	41.5	73	41.7	39.3	42.0
19	34	44.8	15	45.8	42.4	45.2
20	32	48.7	17	49.6	45.5	48.4
21	63	51.6	37	51.1	48.6	51.7
22	115	54.7	73	54.1	51.8	55.0
23	121	57.2	65	57.1	54.9	58.2
24	27	59.8	12	59.6	58.0	61.4
25	21	63.8	16	63.2	61.0	64.5
26	63	66.8	35	67.2	64.0	67.6
27	124	70.3	69	69.8	66.9	70.6
28	106	71.8	62	71.4	69.7	73.5
29	23	72.8	13	74.4	72.4	76.3
30	19	78.6	11	76.8	75.0	78.9
31	53	80.0	30	79.8	77.4	81.4
32	116	82.4	66	81.8	79.7	83.8
33	107	83.6	61	83.3	81.8	85.9
34	29	85.5	14	86.5	83.7	87.9
35	19	87.0	12	87.0	85.3	89.7
36	51	89.3	28	90.2	86.8	91.2
37	104	90.7	56	89.8	88.0	92.5
38	63	91.5	41	90.1	88.9	93.6
39	14	91.1	6	92.3	89.6	94.4

Abbreviations: BPD, biparietal diameter; HIV, human immunodeficiency virus.

Table 7.3. Fetal HC by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st standards.

Gestational age (weeks)	HIV-negative (N=389)		HIV-positive (N=223)		INTERGROWTH-21st standards	
	Number of scans	Mean HC (mm)	Number of scans	Mean HC (mm)	10th centile (mm)	50th centile (mm)
15	31	109.9	21	111.4	102.8	110.4
16	54	124.3	34	122.8	114.9	122.9
17	108	135.7	65	136.1	127.0	135.4
18	134	147.0	73	145.8	139.1	147.9
19	34	159.1	15	161.7	151.1	160.3
20	32	172.0	17	174.9	163.0	172.5
21	63	183.9	37	182.0	174.7	184.5
22	115	194.6	73	193.3	186.2	196.3
23	121	203.1	65	203.2	197.5	207.8
24	27	213.9	12	211.4	208.5	219.1
25	21	226.0	16	226.2	219.1	230.0
26	63	237.8	35	239.5	229.5	240.5
27	124	248.3	69	247.7	239.4	250.7
28	106	255.2	62	253.8	248.9	260.4
29	23	261.3	13	264.1	258.0	269.6
30	19	276.8	11	272.9	266.5	278.4
31	53	283.5	30	284.4	274.6	286.6
32	116	291.0	66	288.9	282.1	294.4
33	107	296.5	61	293.5	288.9	301.5
34	29	301.8	14	305.0	295.2	308.1
35	19	308.9	12	308.6	300.8	314.1
36	51	314.5	28	316.9	305.6	319.4
37	104	319.3	56	316.8	309.8	324.1
38	63	324.3	41	319.0	313.1	328.1
39	14	319.2	6	326.0	315.7	331.4

Abbreviations: HC, head circumference; HIV, human immunodeficiency virus.

Table 7.4. Fetal AC by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st standards.

Gestational age (weeks)	HIV-negative (N=389)		HIV-positive (N=223)		INTERGROWTH-21st standards	
	Number of scans	Mean AC (mm)	Number of scans	Mean AC (mm)	10th centile (mm)	50th centile (mm)
15	31	89.3	21	92.5	85.8	91.9
16	54	101.9	34	100.8	96.3	103.2
17	108	111.6	65	112.9	106.7	114.4
18	134	122.4	73	120.6	117.2	125.6
19	34	132.9	15	135.3	127.6	136.7
20	32	145.0	17	146.9	138.0	147.7
21	63	154.9	37	154.1	148.3	158.7
22	115	166.3	73	168.4	158.6	169.6
23	121	175.1	65	174.8	168.9	180.4
24	27	183.2	12	183.5	179.0	191.2
25	21	195.5	16	197.0	189.1	201.8
26	64	205.4	35	209.4	199.1	212.4
27	124	218.4	69	219.0	209.1	222.9
28	106	228.9	62	227.1	218.8	233.3
29	23	231.8	13	237.9	228.5	243.6
30	19	250.1	11	250.0	238.0	253.8
31	53	260.4	30	256.6	247.4	263.9
32	116	269.1	66	268.0	256.5	273.9
33	107	276.9	61	277.9	265.5	283.8
34	29	289.7	14	295.0	274.3	293.6
35	19	297.2	12	294.0	282.8	303.3
36	51	306.9	28	310.0	291.0	312.8
37	104	317.4	56	317.4	299.0	322.3
38	63	323.0	41	329.3	306.7	331.6
39	14	325.9	6	326.2	314.1	340.8

Abbreviations: AC, abdominal circumference; HIV, human immunodeficiency virus.

Table 7.5. Fetal FL by gestational age and maternal HIV status compared to the 10th and 50th centiles of the INTERGROWTH-21st standards.

Gestational age (weeks)	HIV-negative (N=389)		HIV-positive (N=223)		INTERGROWTH-21st standards	
	Number of scans	Mean FL (mm)	Number of scans	Mean FL (mm)	10th centile (mm)	50th centile (mm)
15	31	16.7	21	16.6	14.3	16.3
16	54	19.5	34	19.4	17.4	19.5
17	108	22.5	65	22.9	20.4	22.5
18	134	25.3	73	25.2	23.4	25.5
19	34	28.4	15	28.8	26.2	28.5
20	32	32.0	17	32.1	29.0	31.3
21	63	33.7	37	33.8	31.7	34.1
22	115	36.8	73	37.1	34.4	36.7
23	121	39.0	65	38.7	36.9	39.4
24	27	42.0	12	41.1	39.4	41.9
25	21	44.4	16	44.4	41.8	44.4
26	64	46.6	35	46.4	44.1	46.7
27	124	48.7	69	48.7	46.4	49.0
28	106	50.2	62	50.8	48.6	51.3
29	23	52.9	13	52.9	50.6	53.4
30	19	56.4	11	56.3	52.6	55.5
31	53	57.5	30	57.3	54.6	57.5
32	116	59.2	66	59.5	56.4	59.4
33	106	60.6	61	60.5	58.2	61.3
34	29	63.9	14	64.2	59.8	63.1
35	19	64.6	12	64.4	61.4	64.8
36	51	66.9	28	67.1	62.9	66.4
37	104	67.8	56	68.4	64.3	67.9
38	63	68.9	41	68.8	65.6	69.4
39	14	71.2	6	70.8	66.9	70.8

Abbreviations: FL, femur length; HIV, human immunodeficiency virus.

Appendix 7.3

Maternal HIV status and newborn anthropometry

Table 7.6. Adjusted associations between maternal HIV status and newborn head circumference and length.

Neonatal anthropometrics	HIV-negative (N=356)	HIV-positive (N=207)	Adjusted β (95% CI)[§] for treated HIV-positive (ref: HIV-negative)
Head circumference (cm), median (IQR)	34 (33, 35)	34 (32.5, 35)	-0.18 (-0.58, 0.21)
Head circumference Z-score[ǀ], median (IQR)	0.42 (-0.33, 1.26)	0.28 (-0.47, 1.11)	-0.14 (-0.36, 0.08)
Newborn length (cm), median (IQR)	48.4 (46.6, 50.4)	48.1 (46, 50)	-0.29 (-0.99, 0.41)
Newborn length Z-score[ǀ], median (IQR)	-0.27 (-1.07, 0.78)	-0.35 (-1.34, 0.69)	-0.13 (-0.40, 0.14)

[§] Adjusted for maternal age, education, marital status, smoking, alcohol consumption, socio-economic status, pre-pregnancy body mass index, parity, history of adverse perinatal outcomes and fetal sex.
[ǀ] Using the INTERGROWTH-21st Newborn Size Standards as a reference.
Abbreviations: β, beta coefficient; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range.