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THE IMPACT OF *IN-UTERO* HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) EXPOSURE ON INFANT OUTCOMES

Karin van der Merwe

WitsETD

Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2010

DECLARATION

I, Karin van der Merwe, declare that this thesis is my own work. It is being submitted for the degree of Master of Science in Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

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DEDICATION

Dedicated to my husband, Michael and my children, Scott and Jody who have given me immeasurable support throughout this process and Professor Ashraf Coovadia who has been my mentor and source of inspiration.

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PUBLICATIONS AND PRESENTATIONS

1. **A model for providing efficient care of pregnant women requiring HAART (Highly Active Antiretroviral Treatment).** van der Merwe, Karin; Coovadia, Ashraf; Technau, Karl; Malan, Eloise; Barry, Gill. Oral presentation*. 2nd South African AIDS Conference*. ICC Durban, 7-10 June 2005.

2. **Integration of antiretroviral treatment within antenatal care in Gauteng Province, South Africa.** van der Merwe, Karin; Chersich, Matthew; Umurungi, Yvonne; Conradie, Francesca; Coovadia, Ashraf. *J Acquir Immune Defic Syndr.* Volume 43, Number 5, December 15, 2006

3. **The effect of *in-utero* exposure to HAART on infant birth weights in a routine clinical setting in South Africa.** van der Merwe, Karin; Black, Vivian; Chersich, Matthew; Technau, Karl; Coovadia, Ashraf; Rees, Helen. Poster Presentation: A197 527, *3rd South African AIDS Conference.* ICC Durban, 5-8 June 2007

4. **The impact of *in-utero* antiretroviral (ART) exposure on infant outcomes in Johannesburg, South Africa.** van der Merwe, Karin;

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Chersich, Matthew; Black, Vivian; Technau, Karl; Rees, Helen; Coovadia, Ashraf. Poster Presentation: WEPEB262, *IAS 2009: 5thIAS Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, 19-22 July 2009

5. **Impact of antiretroviral therapy regimen and duration of therapy on risk of mother-to-child HIV transmission in Johannesburg, South Africa.** Hoffman, Risa; Black, Vivian; Technau, Karl; van der Merwe, Karin; Currier, Judith; Chersich, Matthew; Coovadia, Ashraf. Poster Presentation: WEPEB260. *IAS 2009: 5thIAS Conference on HIV Pathogenesis, Treatment and Prevention*. Cape Town, 19-22 July 2009

6. **Effects of Highly Active Antiretroviral Therapy duration and regimen on risk for mother-to-child transmission of HIV in Johannesburg, South Africa** Hoffman, Risa; Black, Vivian; Technau, Karl; van der Merwe, Karin; Currier, Judith; Coovadia, Ashraf; Chersich, Matthew. J Acquir Immune Defic Syndr 2010. 54(1): p. 35-41.

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ABSTRACT

Background

To investigate whether *in-utero* exposure to highly active antiretroviral treatment (HAART) is associated with low birth weight and/or preterm birth in a population of South African women with advanced HIV infection.

Methods

A retrospective observational study was performed on women with CD4 cell counts ≤250 cells/mm^3 attending antenatal antiretroviral clinics at two clinics in Johannesburg between October 2004 and March 2007. Low birth weight (<2.5kg) and preterm birth rates (<37 weeks) were compared in those exposed versus unexposed to HAART during pregnancy. Effects of different HAART regimen and duration (<28 weeks or ≥ 28 weeks) were assessed.

Results

Among HAART-unexposed infants 27% (60/224) were low birth weight (LBW) compared to 23% (90/388) of early HAART-exposed and 19% (76/407) of late HAART-exposed infants (*P*=0.05). In the early HAART group, older maternal age was associated with LBW and higher CD4 cell count protective against LBW (AOR 1.06, 95% CI 1.00- 1.12 and AOR 0.58, 95% CI 0.46-0.73, P<0.001, respectively). HAART-exposed infants had an increased risk of preterm birth

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(<37 weeks) (15% [138/946] versus 5% [7/147], p=0.001), with early (<28 weeks) nevirapine and efavirenz having the strongest associations with preterm birth (AOR 5.4, 95%CI 2.1-13.7, *P*<0.001 and AOR 5.6, 95%CI 2.1-15.2, *P*=0.001, respectively).

Conclusion

Among infants born to women with CD4 cell counts <250 cells/mm^3, HAART exposure was associated with preterm birth, but not with low birth weight. More advanced immunosuppression was a significant risk factor for both LBW and preterm birth, highlighting the importance of earlier HAART initiation in pregnant women, both to optimize maternal health and to improve infant outcomes

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NOMENCLATURE

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Syndrome
AGA	Appropriate for Gestational Age
ANRS	Agence Nationale de Recherches sur le Sida et les hépatitis virales
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
AZT	Zidovudine
BMI	Body Mass Index
CDC	Center for Disease Control
CI	Confidence Interval
ECS	European Collaborative Study
EFV	Efavirenz
ELISA	Enzyme- linked Immunosorbent Assay
HAART	Highly Active Antiretroviral Therapy (Triple Therapy)
HIV	Human Immunodeficiency Virus
IUGR	Intrauterine Growth Restriction
IL	Interleukin
IL-10-Env	Interleukin 10 Envelope
IL-2-Env	Interleukin 2 Envelope
JH	Charlotte Maxeke Johannesburg Academic Hospital
LBW	Low Birth Weight (less than 2.5kg)
LGA	Large for Gestational Age
MTCT	Mother to child transmission (of HIV)
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
NVP	Nevirapine

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PCR	Polymerase Chain Reaction
PEPFAR	President's Emergency Plan for Aids Relief
PI	Protease Inhibitor (lopinavir/ritonavir in this study)
PMTCT	Prevention of Mother to Child Transmission of HIV
PSD	Pediatric Spectrum of Disease Study
RM	Rahima Moosa Mother and Child Hospital
RPR	Rapid Plasma Reagin
SD	Standard Deviation
SGA	Small for gestational age
STD	Sexually Transmitted Disease
TB	Tuberculosis
UK	United Kingdom
UNICEF	United Nations Children's fund
US	United States of America
VL	Viral Load (of HIV)
VLBW	Very Low Birth Weight (less than 1.5kg)
WHO	World Health Organization
WITS	Women and Infants Transmission Study

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CHAPTER 1

1.0 INTRODUCTION

1.1 CONTEXT

The HIV epidemic in South Africa remains one of the fastest growing epidemics in the world. Currently about one third of all women attending antenatal clinics in the province of Gauteng are HIV seropositive [1]. This has a significant impact on women, children and their families in these communities. Not only are the unborn children at risk of acquiring HIV infection from their mothers, but the social, economic and health effects of HIV undermine the women's' ability to care for their families. In addition, AIDS is the leading cause of maternal mortality in South Africa [2]. This leaves many children orphaned, posing a huge burden on extended families and communities at large.

Use of triple-combination antiretroviral regimens also known as Highly Active Antiretroviral Therapy (HAART) in HIV-infected pregnant women has been shown to decrease mother-to-child transmission of HIV (MTCT) [3]. Moreover, HAART use in pregnancy reduces maternal morbidity and mortality with consequent benefits for infants [4].However, the effects of HAART exposure on foetal and child development remain unclear. As an increasing number of South African women become pregnant while receiving HAART or are started on HAART

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during pregnancy, it becomes important to understand effects of HAART on the foetus.

1.2 LITERATURE REVIEW

1.2.1 Ten years of conflicting studies: Does HAART exposure cause preterm birth? 1998 - 2008

1998 - 2004

The first association between preterm birth (birth before 37 weeks gestation) and combination antiretroviral treatment (HAART) during pregnancy was detected in 1998, in a small retrospective Swiss study of 30 women of whom 10 had preterm births [5]. Subsequently, in 2000, the combined results of the European Collaborative Study and Swiss Mother and Child HIV Cohort Study (3920 mother-child pairs) showed that mothers treated with HAART containing a Protease Inhibitor (PI) were 2.6 fold more likely to have a preterm delivery than untreated mothers [6]. The European Collaborative (ECS) study group updated their findings in 2004 to include 4372 live births. An association between antenatal HAART use initiated pre-pregnancy and preterm birth (AOR 2.05, 95%CI 1.43, 2.95), particularly severe preterm birth (before 34 weeks gestation) was demonstrated. The ECS also detected a high mortality rate associated with delivery at an early gestational age (7.37% at <34 weeks gestation) [7].

In contrast to the above, a 2002 combined cohort analysis of 7 US studies (US combined cohort [8]) among HIV-infected women (2123 women who received

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some form of ART and 1143 women who did not receive ART) did not show an increased risk of low birth weight or preterm birth in women who received ART. Women who received PI-containing regimens were not more likely to have preterm births than those on other regimens [8]. The high prevalence of intravenous drug use (also a cause of preterm delivery) amongst the HIV-infected women from this study may have confounded outcomes [8].

2006

In a 2006 article, Cotter et al attempted to answer the question: “Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth?” by conducting a prospective, single site study in Miami of 1337 HIV positive pregnant women from 1990 to 2002 [9]. Like the ECS, Cotter found that combination therapy with a PI was associated with an increased risk of preterm birth when compared to monotherapy or combination therapy without a PI. There was no difference in numbers of infants with low birth weight across the categories of therapy [9]. Interestingly, some of the patients from this study were part of the US combined cohorts study which found that ART was not associated with preterm birth[8]. Cotter explained this conflicting outcome was probably due to the way patients were selected for the multisite study, which excluded many of the Miami study patients and mentioned that a limitation of multisite collaborations is management of patients by different physicians at different sites, and the retrospective collection of data [9]. The Miami study aimed to investigate the relationship of ART and preterm birth in a single site managed by maternal-foetal medicine sub specialists adhering to strict

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protocols and unified standards of care[9]. Women who received PIs had given birth more recently, had lower CD4 cell counts and a more advanced stage of HIV disease which could have confounded pregnancy outcomes. However, after adjusting for year of delivery, race, prior preterm birth, lowest CD4 in pregnancy, CDC stage, duration of therapy, illicit drug use, smoking, alcohol use and presence of STD, only combination therapy with a PI was associated with an increased risk of preterm delivery (AOR 1.8 [CI,1.1-3.0]), compared with any other combination [9]. There was no increase in the rate of extreme preterm birth (<33 weeks) in women receiving a PI, possibly because of decreased exposure time [9].The authors believe that in pregnancy, PIs should be used with caution due to the increased morbidity and the increased risk of perinatal transmission of HIV associated with preterm birth [9, 10].

In response to this study, Tuomala and Yawetz reviewed the literature in a 2006 editorial [11] in an attempt to tease out the issues causing discrepant results in the studies to date. See table 1.1 for studies included in the analysis:

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Table 1.1 Comparison of studies included in Metanalysis by Tuomala et al [11]

Study	Period	Cohort size	Location	Association between HAART and preterm birth	Limitations mentioned in article	Advantages mentioned in the article
Mandelbrot et al [12]	1994-1998	1344	France	No	None mentioned	None mentioned
Swiss Cohort Study Lorenzi et al [5]	1996-1998	37	Switzerland	Yes	None mentioned	None mentioned
ECS + Swiss [13]	1986-2000	3920	Europe	Yes	Did not control for prior preterm birth PIs typically reserved for more advanced HIV Did not control for HIV stage	Controlled for duration of PI
ECS [13]	1985-2001	2414	Europe	Yes		
ECS Thorne et al [7]	1986-2004	2669	Europe	Yes		
7 US Combined cohorts Tuomala et al [8]	1990-1998	3266	United States	No	Did not control for duration of PI PIs typically reserved for more advanced HIV Did not control for HIV stage	Controlled for prior preterm birth
WITS Tuomala et al [14]	1990-2002	2543	United States	No	PIs typically reserved for more advanced HIV Multiple clinical sites	Controlled for prior preterm birth Controlled for HIV stage Controlled for VL prior to delivery
Morris et al [15]	1997-2001	233	United States	No	None mentioned	None mentioned
Cotter et al [9]	1994-2006	999	United States (Miami)	Yes	Did not control for VL prior to delivery	Controlled for duration of PI Controlled for prior preterm birth Controlled for HIV stage Entire population from one site

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In general, the analyses of data from European Cohorts demonstrated an association between preterm birth and combination ART, but those in United States and France showed no association [11]. The exception was the study by Cotter et al [9] which was the first US analysis which showed an association between combination ART and preterm birth. The discrepancy in results has been ascribed to inherent differences in patient population, differences between providers in choice of ART and use of elective caesarean section, and differences in study methodology and data analysis [11]. The ECS and Swiss Cohort studies did not control for prior preterm birth, a major risk factor for preterm birth. Studies which did control for prior preterm birth include: US combined cohorts [8], WITS (Women and Infants Transmission Study) [14] and Cotter [9]. Duration of PI use was controlled for in ECS but not the US combined cohort. Clinical disease stage, CD4 cell count and HIV load were controlled for in the studies by WITS and Cotter. These two studies had discrepant results with respect to association between preterm birth and ART, the WITS data showing that ART actually protected against preterm birth. The possible reasons for this finding include that the WITS study controlled for HIV load prior to delivery, and that the Cotter study protocol reserved PI use for more advanced stages of HIV disease and failure of virologic control. The ECS study also described reserving PIs for women with more advanced HIV disease. This link between PI-use and advanced HIV disease is considered an important confounding factor for preterm birth [11].

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Tuomala went on to explore the clinical implications of the studies' findings [11]. The majority of preterm deliveries associated with combination ART occurred between 34 and 37 weeks gestation. Preterm births occurring late in the third trimester pose only small risks for neonatal mortality and morbidity in developed countries but the burden to developing countries with less access to neonatal care could be substantial. Preterm birth has also been associated with increased vertical transmission of HIV-1 [10] and significant costs to the health care system.

Tuomala pointed out that a major flaw of all studies up to 2006 is that no study had controlled for stage of maternal HIV disease and satisfactorily addressed the issue of confounding of effect by indication for antiretroviral use during pregnancy [11]. A large randomized, controlled clinical trial aimed at carefully defining risks associated with combination ART regimens used during pregnancy by women receiving ART for foetal protection and whose HIV disease would not otherwise require therapy, is necessary.

Later in 2006, among a population of 681 HIV-1-infected women on HAART in Latin America and the Caribbean, women who received a PI-containing ART regimen during pregnancy had a higher incidence of LBW and preterm birth compared to women who received one or two NNRTIs during pregnancy [16]. However, this association was not significant. This prospective study differed from previous ones in that the primary mode of HIV transmission in Latin America is heterosexual rather than through contaminated needles and intravenous drug use. As a result, the rate of alcohol and illicit substance use during pregnancy was found to be very low. This, as well as lower rates of elective caesarean

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section, could have accounted for the lower overall rate of preterm birth and LBW among HIV-infected women seen in this cohort when compared with the North American and European studies, thus eliminating an important confounding risk factor for preterm birth [16]. With these factors eliminated, PI-exposure was not associated with LBW and preterm birth.

2007

A 2007 population surveillance study of 4445 pregnancies with antiretroviral therapy from 1990 to 2006 in the United Kingdom and Ireland demonstrated an increased risk of preterm birth associated with HAART, but not specifically protease inhibitors, versus monotherapy or dual therapy [17]. After adjusting for ethnicity, age, clinical status and intravenous drug use, women exposed to HAART were 1.51 times more likely to have a preterm infant (<37weeks) (CI 1.19-1.93, *P*=0.001), and 2.34 times more likely to have an extremely premature infant (<35weeks) (CI 1.64-3.37, *P*<0.001) [17].

2007 Metanalysis Findings

A 2007 Meta-analysis of 13 prospective cohorts and one retrospective study showed that HAART during pregnancy did not increase the risk of preterm birth (OR 1.13 CI 0.79-1.63) but that PI-containing combinations resulted in an odds ratio for preterm birth of 1.24 (95% CI 0.76-2.02) compared with combinations without PI [18]. The authors again commented that the use of PI-containing regimens might be more frequent in women with more advanced stage of HIV, in

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itself a risk factor for preterm birth, thus accounting for some of the increased preterm birth observed in this group [18]. In the above studies, historical controls are mostly used for non-ART exposure. This may confound results as understanding of interventions for HIV-infected women during pregnancy have improved with time. A cut off of a gestational age of less than 37 weeks was used as the definition for preterm birth for most studies in the analysis. Data related to more severe degrees of preterm birth would be interesting to examine because of the increased preterm birth-related morbidity and mortality at earlier gestational ages [18]. The results of the meta-analysis could not be adjusted any potential confounding factors contributing to preterm birth because each study controlled for different factors. Factors which the authors would have liked to have adjusted for in the analysis included: maternal CD4 cell count, race, age, illicit drug, alcohol and tobacco use, previous preterm birth, duration of ART during pregnancy and year of delivery [18].

2008

In 2008, data was published from a prospective study in Germany and Austria on the rate of adverse foetal outcomes in 183 mother-child pairs followed from 1990 to 2001. PI-based therapy was associated with an increased risk of preterm delivery (AOR 3.40, 95%CI 1.13-10.2) compared with monotherapy after adjusting for race, maternal age, intravenous drug use, CD4 cell count at delivery and parity [19].

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At the 17th International Aids Conference in Mexico in August 2008, Claire Townsend presented a poster [20] to investigate why an association between preterm birth and use of HAART by HIV-positive mothers has been reported in some studies but not others. A comparison of three studies was undertaken namely: The Pediatric Spectrum of Disease (PSD) [21]; The European Collaborative Study (ECS) [7] and the National Study of HIV Pregnancy and Childhood (NSHPC) [17]. (See Table 1.2 for details of studies). After adjusting for history of injecting drug use, maternal ethnicity, maternal age (except PSD), HIV related symptoms at delivery (except ECS) and child's birth year, the investigators found an association between form of ART (dual or triple therapy) and preterm birth compared to monotherapy across all 3 studies. HAART use (triple therapy) was associated with preterm birth in the ECS and NSHPC but not PSD studies (see table 1.2). Clayden commented that the reason HAART was associated with preterm birth in the UK and European studies and not the US study was possibly because the US study participants had more factors associated with high background preterm birth rates [22]. She postulates that the effect of HAART on preterm birth can only be detected if the background preterm birth rate for patients on monotherapy is low, as in the UK study where the preterm birth rate of patients on monotherapy was similar to the background rate of 6-8% seen in the HIV-negative UK population [22]. This highlights the importance of investigating the association of preterm birth and HAART in the context of the population of interest. This association has not been investigated in the South African context.

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Clayden also pointed out the importance of the duration of HAART exposure in relation to gestational age at time of HAART initiation. This was not fully investigated in the three studies mentioned. She explained there is likely to be a lag between the initiation of therapy and any effect on the foetus. She highlighted the importance of investigating this further as it will impact the timing of HAART initiation for women who do not require HAART for their own health [22].

Table 1.2: comparison of studies by Townsend et al [20]

Study Name	Authors	Time period	Location	Study Type	History of injecting drug use n (%)	Odds ratio for Preterm Delivery (95% CI) *P* value	Summary of findings
PSD - Paediatric Spectrum of Disease [21]	Schulte J, Dominguez K, Sukalac T, Bohannon B, Fowler MG	1990-2004	US	Medical record-based cohort study	1189(13.1)	Monotherapy 1.00 Dual Therapy 0.79 (0.64-0.97) 0.025 HAART 1.01 (0.87-1.16) 0.931	ART was associated with preterm birth compared to monotherapy. HAART had no significant increase in preterm birth.
ECS - European Collaborative Study [7]	Thorne,C: Rudin,C: Newell,M et al	1990-2006	26 centres in 9 European Countries	Consented Cohort Study	1460(35.5)	Monotherapy 1.00 Dual Therapy 0.94 (0.65-1.37)0.765 HAART 1.64(1.3-2.07)<0.001	ART was associated with preterm birth compared to monotherapy. HAART showed significant increase in preterm birth
NSHPC - National population-based surveillance study [17]	Townsend,C: Cortina-Borja,M; Peckham,C: Tookey,P	1990-2006	UK	National population-based surveillance study	295(4.4)	Monotherapy 1.00 Dual Therapy 1.04 (0.59-1.83)0.888 HAART 1.47(1.15-1.87)0.002	ART was associated with preterm birth compared to monotherapy. HAART showed significant increase in preterm birth

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Summary of published literature (1998-2008)

Table 1.3: Major studies showing a link between preterm birth or low birth weight and HAART exposure:

Study	Year of publication	Population	Findings
European Collaborative and Swiss Mother and child HIV cohort study [5]	1998	3920 mother-child pairs in Europe	Protease inhibitor exposure associated with preterm birth
European Collaborative study [7]	2004	4372 live births in Europe	ART-initiation pre-pregnancy associated with preterm birth especially extreme preterm birth
Miami study, Cotter et al [9]	2006	1337 women in Miami	Protease inhibitor exposure associated with preterm birth
National Population-based surveillance study, Townsend et al [17]	2007	4445 pregnancies in UK and Ireland	HAART exposure associated with preterm birth especially extreme preterm birth

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Table 1.4: Major studies showing no link between preterm birth or low birth weight and HAART exposure

Study	Year of publication	Population	Findings
US combined cohort [8]	2002	3266 women in the US	No association between LBW or preterm birth and HAART exposure
WITS [14]	2005	2543 women in the US	Preterm birth decreased in association with HAART exposure
Szyld et al [16]	2006	681 women in Latin America and the Caribbean	PI-exposure not associated with LBW or preterm birth compared to NNRTI exposure
Paediatric Spectrum of Diseases [21]	2007	11 321 infants in the US	HAART not associated with preterm birth

Studies to date have mainly taken place in developed countries where HAART is being used in pregnancy as a PMTCT intervention, regardless of maternal CD4 cell count and stage of HIV disease, with the option of post-partum discontinuation of HAART [5, 7-9, 18]. Additionally in these published studies many women acquire HIV from IV drug use and many pregnant women smoke, confounding the preterm birth outcome. Further study of data representing different ethnic and geographical populations of pregnant HIV-infected women are necessary [18].

The exact PI used in previous studies is not mentioned except in the studies by Lorenzi [5] and Cotter [9] which specify unboosted PIs such as nelfinavir and saquinavir as the main PIs used. The effects of in-utero exposure to boosted PIs, for instance Lopinavir boosted by Ritonavir (Kaletra®), have not been published.

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1.2.2 African Literature

There is limited data from Africa exploring HAART and birth outcomes. A study in Abidjan, Côte d'Ivoire in 2008 [23] compared women eligible for HAART from two sequential cohorts -the ANRS Ditrame plus (March 2001- July 2008) and MTCT-plus projects (August 2003 – August 2007). The former cohort (175 women) received short course ART for PMTCT (mainly short course AZT and single dose NVP) and the latter cohort (151 women) received HAART (Mainly AZT, 3TC and NVP). The rate of LBW was 22.3% in the HAART group and 12.4% in the short course ART group (*P*=0.02). HAART initiated before pregnancy (AOR 2.88, 95%CI 1.10- 7.51) and during pregnancy (AOR 2.12, 95%CI 1.15-4.65) and low maternal BMI at delivery were associated with LBW [23]. Infants were followed up until 1 year of age and neither LBW nor maternal exposure to HAART was statistically associated with infant mortality in HIV-uninfected infants [23]. Weaknesses of the study included the inability to determine preterm birth rates in the data set, the inability to examine the relationship between the duration of ART or HAART exposure and LBW and that confounding variables such as smoking, alcohol and illicit substance use were not taken into account. A strength of the study was that maternal WHO clinical stage and CD4 cell count were controlled for [23].

Another African study took place in four facilities in Botswana between October 2007 and June 2008 [24, 25]. The study included 5676 live births, 1629 of which had an HIV positive mother, and 239 received HAART antenatally. In multivariate analysis, HAART was associated with small for gestational age (SGA) infants

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and this association remained after adjustment for CD4 cell count. The risk of adverse birth outcome according to HAART regimen was not explored. Interestingly, the investigators also found that hypertensive complications at delivery were more common among women who received HAART from prior to the current pregnancy (*P*=0.02) [24, 25]. The possible link between hypertension, HAART and preterm birth is explored later in this dissertation.

1.3 BACKGROUND

1.3.1 Low birth weight

Normal birth weight varies between 2.5kg and 4kg. Infants weighing less than 2.5kg are classified as low birth weight (LBW), infants weighing less than 1.5kg as very low birth weight (VLBW) and infants weighing less than 1kg as extremely low birth weight (ELBW) [26].

LBW contributes to infant and childhood morbidity and mortality. A direct correlation between the LBW rate and infant mortality rate in many countries has been found [26]. LBW and premature infants are at risk for multiple organ system complications, including respiratory, cardiovascular, haematologic, gastrointestinal, metabolic-endocrine, central nervous system and renal [26]. Among VLBW infants, morbidity is inversely related to birth weight.

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Figure 1 Morbidity of VLBW infants according to birth weight

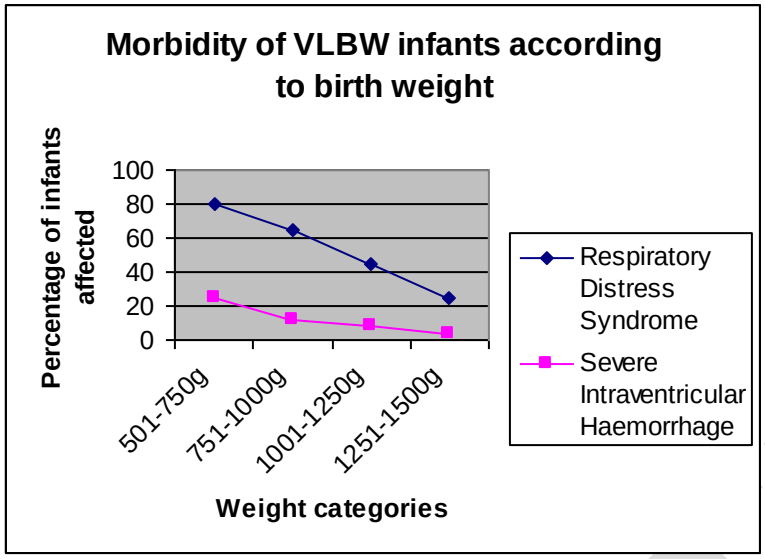


*Figure made using data from Nelson's Textbook of Pediatrics [26]

VLBW infants are at high risk for late sepsis (24%), intraventricular haemorrhage (11%), bronchopulmonary dysplasia (23%), necrotizing enterocolitis (7%) and prolonged hospitalisation (45-125 days). Foetal growth has also been identified as a risk factor for cognitive disability and neurodevelopmental impairment later in childhood. Poor postnatal growth is an important association of preterm and LBW infants [26-28].

Substantial resources at hospital level are required to take care of LBW and premature infants. These infants, particularly if they are VLBW or extremely premature, often require prolonged admission in an intensive care unit (ICU) for parenteral nutrition, fluid balance, respiratory support, thermal regulation, treatment and monitoring of infections and referral for specialized care [26]. This places a burden on the already stretched health care systems of developing countries.

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Epidemiology and Causation of low birth weight

Low birth weight is caused by preterm birth or intrauterine growth restriction (IUGR) or both. Preterm birth is the predominant cause of LBW in industrialized countries whereas developing countries have IUGR as the predominant cause [26]. Rates of LBW are lower in industrialized countries than developing countries. When LBW rates are more than 10%, IUGR is often the predominant cause of LBW [26]. In 2007 according to UNICEF, South Africa had a LBW rate of 15% [29]. This is slightly higher than the USA's LBW rate of 12-13%, which has increased over the last 10 years due to assisted reproductive technology [28]. Other developed countries in Europe report LBW rates as low as 5-9% [28].

LBW due to IUGR can also be divided into asymmetrical and symmetrical growth restriction. In asymmetrical growth restriction the infant's weight is affected more than the skeletal structure which results in the weight and length being on a lower centile (according to gestational age) than the head circumference. This is associated with factors which affect foetal growth late in pregnancy. Symmetrical growth restriction is caused by factors which operate over the entire pregnancy and affects the head circumference, length and weight of the infant equally [26].

It is difficult to completely separate factors associated with preterm birth and IUGR because both have multifactorial aetiologies which involve complex interactions between foetal, placental, uterine and maternal factors.

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LBW has been linked to black race, low or high maternal age, poor economic status, low educational status, single marital status, small parental size, interval between pregnancies of less than six months and mother's parity more than four. Male infants are about 100g heavier than female infants. Socio-economic deprivation of the parents has been specifically linked to a slower rate of foetal growth late in pregnancy resulting in asymmetrical growth restriction [26-28].

1.3.2 Preterm birth

Causation of preterm birth

Preterm birth of infants with a weight that is appropriate for gestational age is associated with factors which abruptly interfere with the ability of the uterus to retain the foetus. These factors could operate by causing rupture of amniotic membranes, stimulating uterine contractions or premature separation of the placenta. A major cause of preterm birth is overt or asymptomatic bacterial infection of the amniotic fluid and membranes. In general causes can be divided as follows [26, 28]:

1) Foetal - multiple gestation, foetal distress, erythroblastosis and non immune hydrops.
2) Placental - placenta previa and abruptio placentae.
3) Uterine - Incompetent cervix and bicornuate uterus.
4) Maternal –
    - pre-eclampsia

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- chronic medical condition (e.g. malnutrition, obesity, hypertension, diabetes, thyroid disease, anaemia and asthma)
- infection (amniotic infections, genital tract infections [especially bacterial vaginosis, Chlamydia, gonorrhoea and syphilis] and systemic infections [including HIV and malaria])
- substance use (smoking, heavy alcohol use, illicit substance use)
- psychological stress.

5) Other - premature rupture of membranes, polyhydramnios, iatrogenic, trauma.

1.3.3 Intrauterine growth restriction

IUGR results in the birth of infants who have lower weights at birth than would be expected for their gestational age. Small for gestational age (SGA) is defined as having a birth weight which falls below the 10th centile of the weight range for a particular gestational age.

Causation of intrauterine growth restriction

IUGR is associated with medical conditions which interfere with the growth of the foetus over a period of time. There is much overlap between the causes of IUGR and preterm birth [26].

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The causes of IUGR can be divided as follows [26, 27]:

1) Placental - low placental weight or surface area, placentitis, infarct, tumour, separation, twin-twin transfusion.
2) Maternal - infection, hypertension, hypoxemia, malnutrition, chronic disease, drugs, alcohol, smoking, environmental exposures.
3) Foetal- chromosomal abnormalities, chronic infections, congenital anomalies, irradiation, multiple gestation, insulin deficiency.

1.3.4 Preterm birth associated with HAART exposure

Immune modulation and preterm birth

A normal pregnancy is characterized by an increase in Th2 cytokines and suppression of Th1 cytokine production. This is because the feto-placental unit produces Th2 cytokines throughout pregnancy which inhibit maternal Th1 cytokines, protecting the pregnancy [30, 31]. The progression of HIV disease is also characterized by a shift from Th1 to Th2 cytokine production [32]. HAART counteracts this cytokine shift [32]. It has been hypothesized that the increased risk for preterm delivery observed in HIV-infected, HAART-exposed women is mediated through changes in the cytokine environment in pregnancy [33]. Fiore et al [33] measured levels of interleukin 2 (IL-2) and interleukin 10 (IL-10), as well as other cytokines (IL-2-PHA, IL-2-Env, IL-10-PHA and IL-10-Env), three times during pregnancy in 49 HIV-infected women. The results showed that HAART use in pregnancy was associated with increased IL-2 (Th1) and decreased IL-10 (Th2). HAART use and IL-10-Env slopes were not significantly associated with

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preterm birth risk, but each unit increase in the IL-2-PHA slope was associated with an 8% increased risk of preterm birth (AOR, 1.08: 95% CI, 1.0-1.17: *P*=0.005). The authors concluded that although HAART had significant benefits in delaying HIV progression and preventing mother-to-child transmission of HIV, it may be associated with negative pregnancy outcomes due to immune modulation.

Pre-eclampsia and preterm birth

Pre-eclampsia was an uncommon complication of pregnancy in the pre-HAART era when HIV positive women were found to be less at risk for pre-eclampsia than their negative counterparts [34]. Pregnant women on HAART are however as likely to experience pre-eclampsia as the general population [35]. One European survey of 36 hospitals from 11 countries has identified pre-eclampsia as the most common adverse event in HAART-exposed women [36]. A Spanish study investigated this further by looking for trends in prevalence of pre-eclampsia and foetal death over 18 years [37]. The study showed a significant increase in the rate of pre-eclampsia in HIV-infected women over a 15 year time period (1985 to 2000) and HAART exposure prior to pregnancy was identified as a risk factor for pre-eclampsia. [37]

Among the 12 HAART-exposed patients in the Spanish study who developed pre-eclampsia or foetal death, 4 (33%) were born before 34 weeks of gestation, 1 (8%) was born between 37 and 34 weeks, and 7 (58 %) were born at or after 37 weeks [37]. The study concluded that HAART prior to pregnancy was associated with a higher risk for pre-eclampsia and foetal death. Insulin resistance and

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endothelial inflammation were identified as potential underlying mechanisms [37]. Although not specifically investigated, the same process could lead to increased risk of preterm deliveries in HAART-exposed women.

Hormonal Modulation

PIs have been shown to decrease the plasma concentrations of exogenously administered ethinylestradiol by PI induction of the hepatic P450 cytochrome enzyme system [38]. It is possible that PIs also disrupt oestrogen and progesterone metabolism in pregnancy causing preterm labour [39].

1.4 THE SOUTH AFRICAN CONTEXT

Compared with other middle-income countries, the South African standard of care for PMTCT prior to 2008 was suboptimal. Only women with CD4 cell counts of 200cells/mm^3 or less or WHO clinical stage IV disease qualified for HAART, as specified by the Department of Health Policy Guidelines [40]. Women who did not qualify for HAART received a single dose of nevirapine (NVP) to be taken at onset of labour followed by a single dose of NVP to the infant within 72 hours of birth [40]. Paradoxically, women at a more advanced stage of disease were therefore less likely to transmit HIV to their infants because they accessed HAART [41]. A 2005 JAIDS paper presenting results from Rahima Moosa Mother and Child Hospital (RM) in Johannesburg documented this paradoxical situation [41].

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South African pregnant women who access HAART differ in important ways from those studied in the Northern Hemisphere. Firstly women receiving HAART antenatally in South Africa are at a later stage of HIV disease than their counterparts in high-income countries. Secondly, HIV Clade C predominates in South Africa as opposed to Clade B in Western Europe and North America. Lastly, HIV infection among South African women is acquired through heterosexual contact rather than through intravenous drug use which was historically the main mechanism of transmission in Europe and America.

Additional evidence of the impact of HAART exposure on infants in our setting is required.

1.5 STUDY OBJECTIVES

The study aims to test the null hypothesis that HAART is not associated with preterm birth. It is designed to determine whether an association exists between HAART and various birth outcomes (preterm birth, low birth weight and others) and to determine the strength of the association. It was conducted in women with low immunity in a South African context.

The specific study objectives are:

1) To compare gestation at delivery and birth weights of infants exposed to HAART during pregnancy with those without such exposure.

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2) To compare gestation at delivery and birth weights of infants exposed to HAART before 28 weeks gestation (early HAART) and those exposed to HAART at or after 28 weeks gestation (late HAART).

3) To compare gestation at delivery and birth weights of infants exposed to PI-based (lopinavir/ritonavir), NVP-based (nevirapine) and EFV-based (efavirenz) regimens.

1.6 ORGANISATION OF THE THESIS

The remainder of this thesis will attempt to explore the impact of *in-utero* HAART exposure on infants.

The methods section will explain the context of study clinics, explain the selection of study participants, define the variables and detail the study design.

The results section will systematically present the study findings covering the following sections:

1. Phase 1: Comparison of study groups in terms of demographics and maternal health status.
2. Phase 2: Comparison of study groups in terms of pregnancy characteristics and infant outcomes.
3. Phase 3: Association of study variables with low birth weight and preterm birth among study infants.

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4. Phase 4: Multivariate logistic regression analysis on the risk factors of LBW and preterm birth in study infants.

The discussion section will attempt to explain the study's findings in the context of the current literature and highlight study limitations.

The conclusion will answer the objectives of the study and highlight the relevance of the study's findings.

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CHAPTER 2

2.0 METHODS

2.1 BACKGROUND

Antenatal HIV clinics of Rahima Moosa (RM) and Charlotte Maxeke Johannesburg Academic (JH) are main referral centres for HIV-infected pregnant women. Women attending Antenatal HIV clinics constitute an ongoing cohort in which HIV-infected women are enrolled and are observed in accordance with standard clinical and laboratory practice of the South African National HIV programme [40, 42]. Using the patient records, we conducted a retrospective observational study. Findings of previous analyses of this cohort have been presented elsewhere [41, 43-46].

2.1.1 Description of study hospitals

RM is a secondary level academic hospital which has a midwife run antenatal clinic for uncomplicated pregnancies as well as an obstetrician run antenatal clinic for complicated pregnancies. JH is a tertiary level academic hospital which mainly manages referrals of complicated pregnancies.

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Description of study clinics

The **antenatal** HIV clinics of Rahima Moosa (RM) and Charlotte Maxeke Johannesburg Academic (JH) were offering the following services at the time of the study:

For all pregnant women:

1) Provider-initiated HIV testing and counselling
2) Essential antenatal care

For all HIV-infected pregnant women

1) CD4 cell count testing
2) HIV Wellness Counselling and implications/interpretation of CD4 cell counts
3) Counselling on infant feeding choices/options
4) Participation in support group for HIV positive pregnant women

For HIV-infected women who do not qualify for HAART:

1) Provision of single dose-NVP
2) Counselling on the signs of labour and use of NVP
3) Referral to postnatal HIV clinic for infant diagnosis.

For the women who qualified for HAART (HAART-exposed)

1) Counselling on benefits of HAART to mother and infant

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2) Counselling on side-effects of HAART
3) Adherence counselling –the importance of taking HAART correctly as prescribed
4) Baseline blood tests according to protocol
5) Initiation of HAART
6) Follow-up of patients on HAART fortnightly for women on nevirapine-based HAART for the first 4 weeks, monthly for lopinavir/ritonavir-based HAART. Women are followed up until approximately ten weeks post partum.
7) Referral to post natal clinic for infant diagnosis and infant formula collection (when applicable).
8) Referral of mother to Adult HIV clinic once infant has been delivered. (Mostly Helen Joseph Hospital, JH, Witkoppen Clinic or Hillbrow Community Health Centre.)

The **Postnatal** (Infant follow-up) HIV clinic of RM Hospital was offering the following services:

1) Maternal CD4 cell count and plasma Viral Load (VL) repeated as per guidelines.
2) Adherence monitoring of women on HAART.
3) For women not yet on HAART who qualify – initiation on HAART at the postnatal clinic or referral to an accredited ARV site.

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4) Infant formula distribution.
5) Infant clinical examination for stigmata of HIV and other abnormalities at 6 weeks post birth.
6) Trimethoprim/sulphethoxazole (Co-trimoxazole) prophylaxis provision to infant pending HIV result.
7) Infant HIV PCR drawn and first clinical assessment at 6 weeks of age.
8) Infant reassessed at 10 weeks of age and results of PCR provided to the caregiver.
9) Infant HIV diagnosis once clinical and laboratory tests conferred [47].
10) Referral of infants testing HIV positive to a Paediatric HIV clinic.

A similar postnatal clinic at JH was started during the study period but patients were not recruited from this clinic.

The study did not involve any further clinical or laboratory interventions over and above the services currently offered by the clinics. The study used data which was routinely collected from the records of clinic patients for the clinic data base or obtained retrospectively from their hospital records.

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2.2 STUDY PARTICIPANTS

The study included all eligible HIV-positive women attending HIV antenatal clinics of RM and JH and the HIV postnatal clinic of RM who gave birth from October 2004 to March 2007, and their infants. The time period was chosen because the clinics began collecting data from October 2004 and the protocol was submitted for ethics evaluation in April 2007.

2.2.1 Inclusion and exclusion criteria

Inclusion criteria

1) Confirmed HIV- infected – either by Rapid HIV test or HIV ELISA test.
2) Presentation to the study clinic during pregnancy or less than 2 months post partum.
3) CD4 cell counts during pregnancy or within 3 weeks post partum of less than or equal to 250cells/mm^3.
4) Singleton pregnancies.
5) Verbal or written consent given for inclusion in the clinic data base.

Exclusion criteria

1) CD4 cell count more than 250 cells/mm^3.
2) Multiple births

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2.2.2 Participant grouping

Women in the study were divided according to the presence (HAART-exposed) or absence (HAART-unexposed) of HAART exposure during pregnancy. The HAART-exposed group was further divided according to the hospital they attended – JH or RM hospitals. HAART-exposed women were also divided according to those who started HAART before 28 weeks of pregnancy (early HAART) and those who started HAART at or after 28 weeks (late HAART).

For each group the key measurable outcomes included birth weight and gestation at delivery. Other associated variables were also analysed.

Women were further stratified into those with infant's HIV PCR status known or unknown. Those with known PCR status were divided into positive and negative status. The group with negative PCR status were then analysed for associations of study variables with low birth weight. Those with unknown or positive status were removed to control for the effect of *in-utero* HIV transmission on birth weight [48].

HAART-exposed group

Most women who received HAART from the study clinics had CD4 cell counts below 250cells/mm^3 due to clinic protocols which were based on Department of Health Guidelines at the time [40]. The few women on HAART with CD4 cell counts above 250cells/mm^3 were excluded from this study

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Protocols for initiation of HAART to pregnant women at the hospitals differed. At RM hospital, pregnant women were initiated on PI-based HAART, namely lopinavir/ritonavir combination (Kaletra®), stavudine (D4T) and lamivudine (3TC) as first line therapy. nevirapine (NVP), D4T and 3TC or efavirenz (EFV), D4T and 3TC and were reserved for women with contra-indications to lopinavir/ritonavir.

At JH hospital, first line therapy was NVP, D4T and 3TC, and the other regimens mentioned were used for patients with contra-indication to NVP. In both hospitals, EFV was initiated mainly when pregnant women were receiving concomitant TB treatment (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) because of drug interactions between TB drugs and lopinavir/ritonavir or NVP. EFV was only initiated beyond the first trimester of pregnancy due to the potential teratogenic effects of EFV on foetal neural tube development [49]. Some women in the study were on EFV at the time of presentation at study clinics. Both hospitals followed the protocol of changing the EFV to lopinavir/ritonavir if women presented in the first trimester. Women who presented after the first trimester were left on EFV but underwent close foetal monitoring including ultrasound examinations to detect foetal anomalies. No foetal anomalies were detected in this group of women in either hospital.

The HAART-exposed group was divided according to first regimen used in pregnancy– NNRTI-based (NVP-based or EFV-based) or PI-based. The purpose of these divisions was to compare the groups in terms of demographics, possible

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confounding variables which could inadvertently cause preterm birth and to compare the birth outcomes of each exposure group.

Most women in the HAART-exposed group accessed antenatal HIV care at the study clinics ante partum (see figure 2). Most HAART-unexposed women presented to the study clinics post partum for infant diagnosis.

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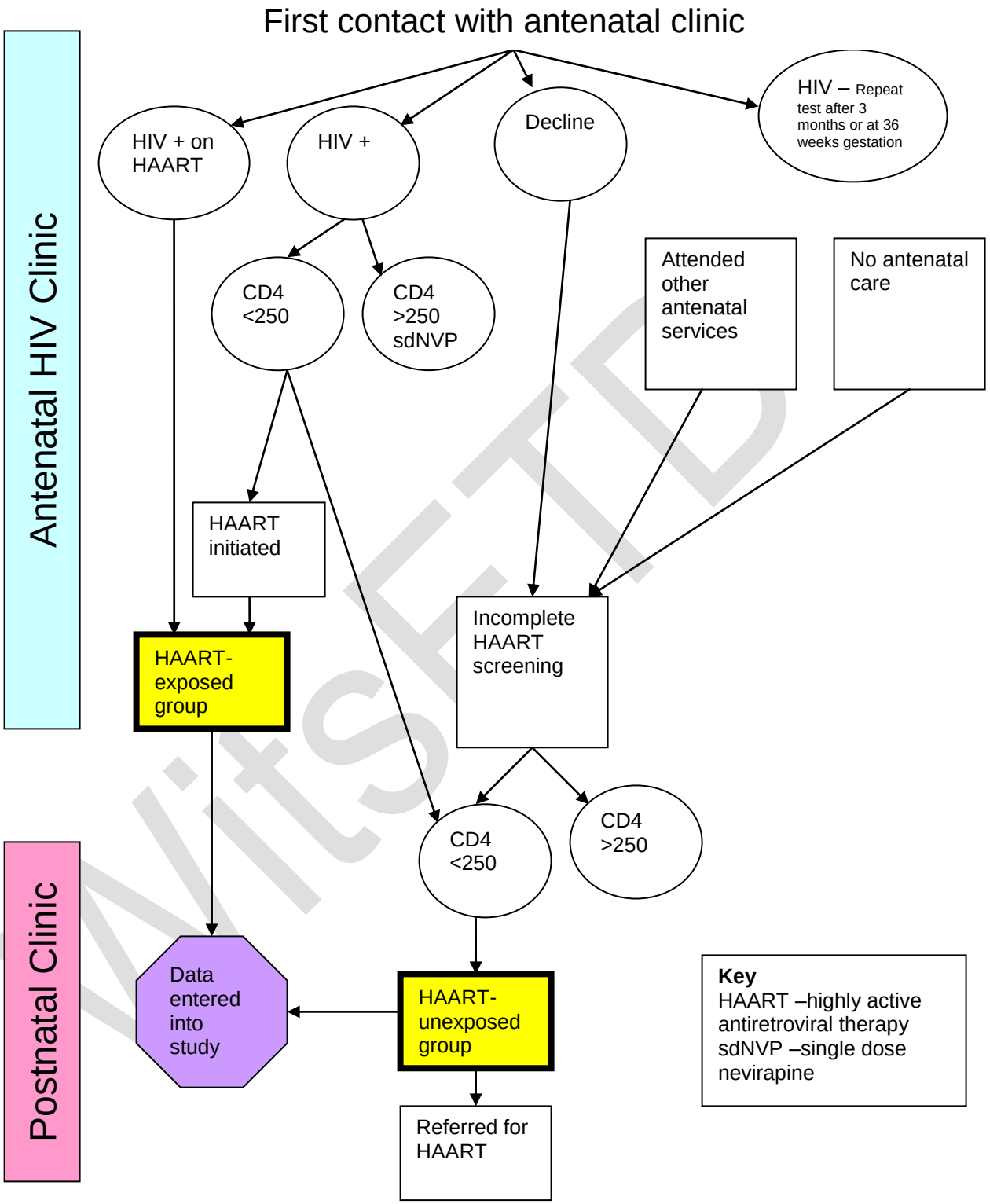


Figure 2 Flow of patients through antenatal and postnatal HIV services to indicate points of entry into the study (highlighted in yellow)

HAART-unexposed group

The unexposed group was drawn from HIV-infected women who did not receive HAART during pregnancy – most having received single dose nevirapine and a few having had no PMTCT opportunity. This control group consisted of HIV positive HAART-unexposed women with CD4 cell counts below 250cells/mm^3 during pregnancy or within three weeks of delivery.

Most of the HAART-unexposed group members had missed the opportunity for HAART because they were identified as HIV positive during admission for delivery and referred to the postnatal clinic where they were found to have low CD4 cell counts. At the time of the study, only the RM hospital had a dedicated postnatal clinic for follow-up of infants exposed to HIV, therefore all of the HAART-unexposed women were from RM hospital. The reasons for their missed opportunities for HAART included:

- Women who had not attended antenatal clinic.
- Women who had attended an antenatal clinic other than the study clinics but had not been diagnosed for HIV by the clinic due to patient refusal or poor health systems.
- Women who had attended an antenatal clinic other than the study clinics and had been diagnosed for HIV but had not been staged using a CD4 cell count due to patient refusal or failure of the health system.
- Women who had attended an antenatal clinic other than the study clinics and had been diagnosed for HIV and found to have a low CD4 cell count

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but had not initiated HAART due to patient refusal or health system failure.

- Women who had attended a study clinic ante partum but had refused HIV diagnosis, HIV staging or HAART initiation.
- Women who had attended a clinic ante partum, and qualified for HAART initiation but had failed to initiate HAART before delivery of the infant due to other urgent health concerns causing unavoidable delays.

2.3 STUDY VARIABLES

Using record review, we conducted a retrospective observational cohort study. The records of the women-infants pairs were reviewed to extract information on the following variables:

Participant grouping:

- Maternal PMTCT regimen i.e. HAART-exposed or HAART-unexposed
- HAART initiation date (used to derive duration of HAART*)
- HAART regimen*(first used in pregnancy)
- Actual date of delivery (used to derive duration of HAART*)
- HIV PCR status of infant –unknown, negative or positive

Demographics:

- maternal date of birth (to derive maternal age*)
- race group*

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Substance use:

- illicit substance use (during pregnancy)
- alcohol usage* (during pregnancy)
- smoking* (during pregnancy)

HIV Disease:

- maternal WHO clinical stage* (during pregnancy)
- lowest maternal CD4 cell count* (during pregnancy or up to 3 weeks post partum)

Health Status:

- hypertension* (systolic blood pressure [BP]>160mmHg or diastolic BP> 90mmHg on 2 occasions 4 hours apart; or 1 diastolic BP> 110mmHg).
- diabetes* (requiring intervention such as medication or delivery),
- anaemia* (haemoglobin less than11gm/dl at any time during pregnancy),
- severe anaemia* (haemoglobin less than 7gm/dl at any time during pregnancy)
- syphilis* (positive RPR)
- Tuberculosis (TB) (requiring medication)
    - TB information only available for JH women
- Reproductive Health:
- gravidity (number of previous pregnancies)

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- previous miscarriage
- previous preterm birth

Pregnancy and Infant outcomes

- mode of delivery
- infant gender
- expected date of delivery (used to derive gestation*)
- actual date of delivery (used to derive gestation*)
- birth weight of infant
- head circumference of infant
- HIV PCR status of infant –unknown, negative or positive

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2.3.1 Explanation of key study variables

Duration of HAART

The duration of HAART was defined as the length of time on HAART from initiation of HAART to delivery.

Gestational age

Gestational age at birth was determined by comparing the expected and actual dates of delivery. Expected date of delivery was determined on the basis of early ultrasound biometry when available. When this was not available, last menstrual period of the mother or clinical measurement of fundal height was used.

Infants born at or after 37 weeks of gestation were classified as term. Infants born before 37 weeks of gestation were classified preterm and those born before 34 weeks, as extremely premature.

Birth weight

Birth weights were obtained from maternal hospital files or information on the infant's "Road-to-health card". This is a patient-held health document of birth history, growth and immunizations issued to all infants born in South Africa at birth.

Infants weighing 2.5kg or more at birth were classified as normal birth weight. Infants weighing less than 2.5kg at birth were classified as low birth weight (LBW) and those weighing less than 1.5kg were classified as very low birth weight (VLBW). Infants weighing less than 1.0 kg are defined as extremely low birth weight (ELBW) but this distinction was not made for the purposes of this study.

Growth

The weight and gestational age of each infant at birth were compared using an foetal-infantile growth chart [50] (appendix 1) to categorise infants into one of 3 groups:

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Small for gestational age (SGA) – those who fell below the 10th centile of expected weight for gestation age.

Appropriate for gestational age (AGA) – those who fell on or between the 10th and 90th centiles of expected weight for gestational age.

Large for gestational age (LGA) – those who fell above the 90th centile of expected weight for gestational age.

2.4 STUDY DESIGN

2.4.1 Study groups (for Phases 1 and 2):

1) HAART-exposed vs. HAART-unexposed – The purpose of this comparison was to investigate the impact of HAART on birth outcomes.
2) Early HAART-exposed vs. late HAART-exposed – The purpose of this comparison was to investigate the impact of the duration of HAART on birth outcomes.
3) Early HAART: PI-based vs. NVP-based vs. EFV-based – The purpose of this comparison was to investigate the impact of regimen on birth outcomes (specifically in women who received a relatively long duration of HAART).
4) Late HAART: PI-based vs. NVP-based vs. EFV-based – The purpose of this comparison was to investigate the impact of regimen on birth outcomes (specifically in women who received a relatively short duration of HAART).

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5) RM HAART-exposed women vs. JH HAART-exposed women – The purpose of this comparison was to investigate for inherent differences in study hospitals in terms of birth outcomes and their risk factors.

2.4.2 Study Phases

Phase 1

In order to contextualise each group and detect inherent differences which have been known to affect infant birth weight and gestation, study groups were compared in terms of demographics, substance abuse, HIV disease, health status and reproductive health [28, 48, 51, 52].

Phase 2

Study groups were compared in terms of risk for specific pregnancy and infant outcomes. Pregnancy outcomes included duration of HAART and mode of delivery. The key Infant outcomes compared were infant weight and gestation. Other associated infant outcomes such as gender, weight for age, head circumference and HIV status were also analysed.

Phase 3

To control for the effect of infant HIV status on birth weight [48]. Infants with known HIV negative status were analysed to detect associations between study variables (see variables with * above) and LBW.

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A further analysis of all infants was done to detect associations between study variables and preterm birth.

Phase 4

Variables associated with LBW or preterm birth in univariate analysis ($P<0.1$) were included in the multivariate model and retained if their removal markedly altered the model fit. Adjusted odds ratios were derived for HAART-exposed women for each of the variables using the HAART-unexposed women as a reference group.

2.5 AUXILLIARY SERVICES

2.5.1 Laboratory services

These services were provided routinely by the NHLS (National Health and Laboratory Service).

Laboratory tests

HIV status was determined at first antenatal visit using 2 Rapid HIV tests – First Response HIV Card test 1-2.0 [Kachigam, Daman, India] and Pareekshak HIV Triline card test [Bangalore, Karnataka, India].

CD4 cell count was determined using a Beckman Coulter (Fullerton, CA) Epics XL MCL cytometer and Beckman Coulter TQ PREP.

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HIV diagnosis was determined in infants aged 6 weeks or older with a DNA polymerase chain reaction (PCR) test (Amplicor HIV-1 DNA PCR version 1.5 assay; Roche Diagnostics, Inc., Alameda, CA) by a locally validated protocol [47].

2.5.2 Data Analysis

Although the author was involved in data interpretation, she was guided by an epidemiologist (Prof. Matthew Chersich).

Initially univariate analysis was done, comparing the risk of study outcomes in different exposure groups. Statistical tests were used to detect an association between exposure variables and study outcomes (chi-square test for categorical variables and Student's t test for continuous exposure variables). The strength of associations detected was shown in odds ratios, with 95% confidence intervals used to demonstrate levels of uncertainty of these estimates. Conversely, when no association was detected, some margin of assurance could be provided that such exposures do not increase odds of preterm birth or low birth weight. The 95% confidence intervals denote such margins of assurance.

Bivariate analysis was also undertaken to compare differences in outcomes in population sub-groups. The duration that HAART was received was categorized, forming a binary variable (early and late HAART exposure). Thereafter an analysis of the effect of HAART exposure on pregnancy outcomes was assessed in each stratum of duration. This allowed for stratum-specific odds ratios to be

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calculated, specifically the odds of LBW in women who received PI-based early HAART (The primary outcome of interest).

Multivariate logistic regression analysis was done, using backward fitting to develop model which best characterizes the data. Variables were retained in the model if their removal markedly altered the model fit. Log-rank tests were used to build and evaluate results of the multivariate model.

Multivariate analyses examined the risk factors for LBW in the group of women who were known to have had PCR negative infants and risk factors for preterm birth in all women. Variables chosen for this analysis included HAART-exposure according to regimen, CD4 category; maternal age and hypertension. The model analysed the odds of LBW according to regimen type: PI-based HAART, NVP-based HAART and EFV-based HAART; each rise in CD4 category (in cells/mm^3): 0-49, 50-99, 100-149, 150-199 and 200-250; each year of increase in maternal age and for the presence or absence of maternal hypertension.

Women exposed to early and late HAART were analysed separately because of interaction within the variable of HAART regimen for instance women exposed to early EFV-based HAART had a much higher odds ratio of LBW than those exposed to late EFV-based HAART.

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Single Data entry was done in Microsoft Access. Intercooled Stata 8.0 (Stata Corporation, College Station, TX, United states) was used for data analysis.

Missing data

Analysis of data was restricted to subjects with a complete data set on the specific variable involved. No imputation of data was performed.

Student's t-tests and chi-squared tests were performed to determine characteristics of women and children with incomplete information. Fisher's exact test was utilized for analysis of categorical variables with sparse data and Wilcox sum rank test was performed when data was skewed. We attempted to evaluate the influence of missing data by performing comparisons among women with and without information on HAART duration to make sure these did not differ significantly.

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2.5.3 Funding

The study did not require any external funding. The clinics where the study took place were funded by the South African Department of Health and are supported by the following NGOs: ECHO (Enhancing Children's HIV Outcomes), RHRU (Reproductive Health and HIV Research Unit), The Elizabeth Glaser Pediatric Aids Foundation and USAID's (United State Agency International Development) PEPFAR (President's Emergency Plan for AIDS Relief) programme.

2.6 ETHICAL CONSIDERATIONS

2.6.1 Patient Consent

Each antenatal and postnatal clinic has a database of attendees to assist with statistical collection for the Department of Health and to monitor and evaluate clinic systems. At RM Hospital, patients were requested to sign a voluntary consent form allowing for use of anonymous data for study purposes (Appendix 2). Patients who did not consent to this were excluded from the study. At JH Hospital women provided verbal consent for inclusion in the database

2.6.2 Confidentiality

Every effort was made to maintain patient confidentiality. The databases were analysed once patient names were removed. Only people directly involved in the study had access to the databases.

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2.6.3 Ethics Approval

The protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand on 07 May 2007. Ethics number: Protocol M070438; R14/49 van der Merwe

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CHAPTER 3

3.0 RESULTS

3.1 STUDY POPULATION BREAKDOWN

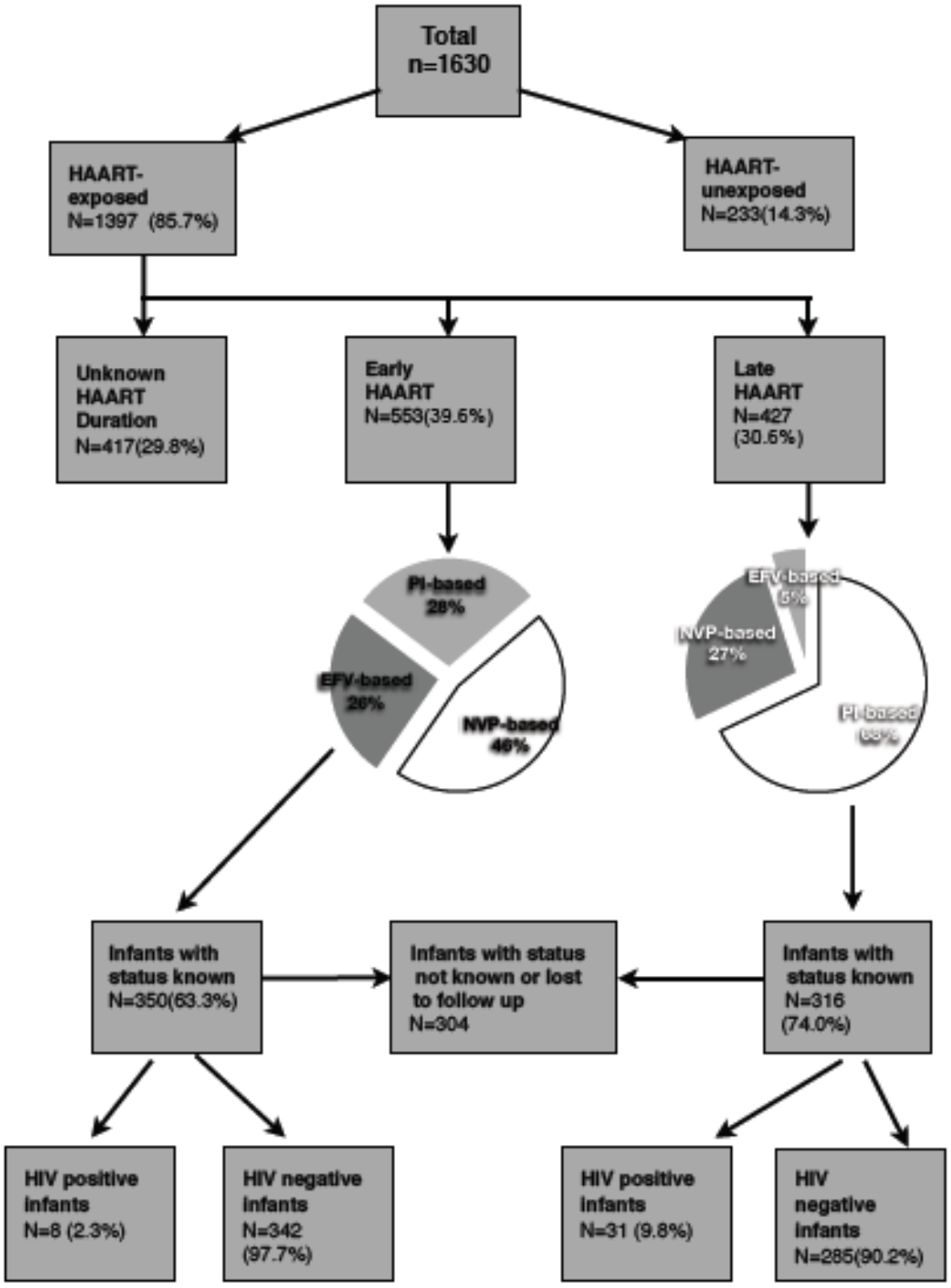
The study comprised 1630 women, 233 (14%) who were unexposed to HAART and 1397 (86%) who received HAART during their pregnancy. In the HAART-exposed group, 49% (690) and 51% (707) of women accessed care at RM and JH hospitals respectively. All of the HAART-unexposed women were from RM.

The HAART-exposed group comprised of 553 (40%) women who were known to have received HAART before 28 weeks of gestation (early HAART) and 427 (30%) women known to have received HAART after 28 weeks of gestation (late HAART). The duration of HAART exposure during pregnancy was unknown for 417 (30%) women.

In the early HAART group, 157 (28%) women received PI-based HAART, 254 (46%) received NVP-based HAART and 142 (26%) received EFV-based HAART. In the late HAART group, 290 (68%) women received PI-based HAART, 116 (27%) received NVP-based HAART and 21 (5%) received EFV-based HAART.

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Figure 3.1 Flow diagram of study population



3.2 DEMOGRAPHICS AND MATERNAL HEALTH STATUS

(Tables 3.1.1, 3.1.2 and 3.1.3)

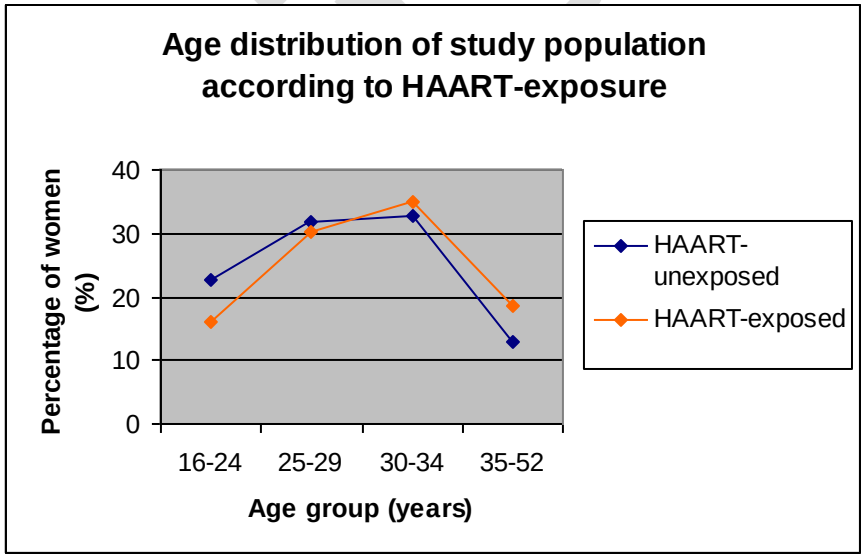
3.2.1 Demographics

Maternal Age

The age of women in the study was available for 77% (180/233) of HAART-unexposed and 98% (1372/1397) of HAART-exposed women. Mean age in the HAART-unexposed group was 28.9 (SD 5.1) which was lower than the HAART-exposed group's mean age of 30.3 (SD 5.1) (*P*<0.001).

The majority of women were between 25 to 34 years of age (65%) with the remaining third of women were almost equally split between the age groups of 16 to 24 years (17%) and 35 to 52 years (18%).

Figure 3.2.1 Age distribution of study population according to HAART-exposure



Mean age of women exposed to HAART at RM and JH (30.2 [sd5.1] vs. 30.4 [sd5.2],) as well as age between early and late HAART exposure (30.6 [sd5.1] vs.

30.1 [sd5.2]) did not differ (*P*= 0.53 and 0.18 respectively). Neither did the mean age of women exposed to different HAART regimens across the groups differ (*P*=0.23 for early HAART and *P*=0.49 for late HAART).

Race Group

Information on race was available for 16% (37/233) of the HAART-unexposed and 50% (694/1397) of the HAART-exposed group. The predominant race across all groups was black - 94% of HAART-unexposed and 98% of HAART-exposed women (P=0.15).

The black race group was more common at JH than RM (99% vs. 92%, P<0.001).

Women exposed to early HAART were more likely to be black than those exposed to late HAART (98% vs. 96%, P=0.016). No white or Indian women were exposed to early HAART versus three who received late HAART. Racial split did not differ according to regimen use.

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Table 3.1.1 Demographics and maternal health status in women exposed and unexposed to antiretroviral treatment and by duration of exposure

Variable category	Variables	HAART-unexposed (A) N=233	HAART-exposed (B) N=1397	*P* value (A vs. B)	Early HAART-exposed (C) N=553	Late HAART-exposed (D) N=427	*P* value (C vs. D)
Demographics	**Maternal age**	N=180	N=1372		N=540	N=426	
	mean years (SD)	28.9 (5.1)	30.3 (5.1)	<0.001	30.6 (5.1)	30.1 (5.2)	0.18
	Race group n (%)	N=37	N=694		N=341	N=125	
	Black	34 (94)	680 (98)		335 (98)	120 (96)	
	mixed ancestry	2 (6)	10 (1)		6 (2)	2 (2)	
	Indian/White	0 (0)	4 (1)	0.15	0 (0)	3 (2)	0.016
Substance use	**Smoked in pregnancy** n (%)	6 (4)	28 (4)	0.69	15 (5)	7 (2)	0.085
	Alcohol use in pregnancy: n (%)	7 (5)	29 (4)	0.51	15 (5)	7 (2)	0.085
HIV disease	**WHO stage** n (%)	N=6	N=744		N=256	N=270	
	stage 1	3 (50)	446 (60)		149 (58)	180 (67)	
	stage 2	1 (17)	94 (13)		33 (13)	35 (13)	
	stage 3	1 (17)	160 (22)		55 (21)	43 (16)	
	stage 4	1 (17)	44 (6)	0.71	19 (7)	12 (4)	0.13
	Immunological status	N=233	N=1397		N=553	N=427	
	CD4 cells/mm^3 n (%)						
	0-49	5 (2)	124 (9)		59 (11)	28 (7)	
	50-99	29 (12)	216 (15)		91 (16)	62 (15)	
	100-149	35 (15)	325 (23)		122 (22)	108 (25)	
	150-199	64 (27)	412 (29)		156 (28)	136 (32)	
	200-250	100 (43)	320 (23)	<0.001	125 (23)	93 (22)	0.12
	mean CD4 cell count	176.0	146.1		141.8	149.9	
	SD	*55.9*	*62.5*		*64.3*	*58.3*	
	median CD4 cell count	191	154		152	155	
	IQR	*136-220*	*101-195*	<0.001	*93-195*	*108-194*	0.12
Health status	**Hypertension in pregnancy** n (%)	18 (12)	93 (10)	0.38	41 (10)	27 (8)	0.32
	Diabetes history n (%)	1 (1)	3 (0)	0.51	1 (0)	2 (1)	0.46
	Haemoglobin (Hb)	N=100	N=912		N=312	N=286	
	Hb <11gm/dl, n (%)	57 (57)	416 (46)	0.03	129 (41)	140 (49)	0.062
	Median Hb gm/dl	10.7	11.1		11.3	11.0	
	IQR	*9.8-11.5*	*9.9 -11.9*	0.019	*10.1-12.1*	*9.9-11.8*	0.007
	Syphilis serology n (%) positive RPR	3 (2)	35 (4)	0.29	11 (4%)	11 (3)	0.60
Reproductive health	**Gravidity** n (%)	N=204	N=954		N=413	N=354	
	1	30 (15)	126 (13)		51 (12)	57 (16)	
	2	83 (41)	351 (37)		142 (34)	140 (40)	
	3	59 (29)	292 (31)		131 (32)	98 (28)	
	≥4	32 (16)	185 (19)	0.50	89 (22)	59 (17)	0.083
	median	2	2		3	2	
	IQR	*2-3*	*2-3*	0.13	*2-3*	*2-3*	0.010
	Previous miscarriage*: n (%)	27 (18)	130 (17)	0.66	70 (22)	38 (12)	0.001
	Previous preterm infant* n (%)	16 (11)	39 (6)	0.055	13 (6)	18 (6)	0.71

All women have a CD4 ≤250cells/mm^3; SD – standard deviation; *IQR* –interquartile range; RPR – rapid plasma reagin
*in women with a previous pregnancy

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Table 3.1.2 Comparison of demographics and maternal health status in women receiving different antiretroviral regimens in pregnancy

Variable Category	Variables	Early HAART-exposed N=553			*P*	Late HAART-exposed N=427			*P*
		PI-based HAART N=157	NVP-based HAART N=254	EFV-based HAART N=142		PI-based HAART N=290	NVP-based HAART N=116	EFV-based HAART N=21	
Demographics	**Maternal age** mean years (SD); n	30.9 (4.8);156	30.2 (5.2);248	31.1 (5.1);136	0.23	30.0 (5.0);290	30.6 (5.6);115	29.5 (5.3);21	0.49
	Race group n (%)	N=33	N=199	N=109		N=35	N=82	N=8	
	Black	32 (97)	198 (99%)	101 (96)		32 (91)	80 (98)	8 (100)	
	mixed ancestry	1 (3)	1 (1)	4 (4)		1 (3)	1 (1)	0 (0)	
	Indian/White	0 (0)	0 (0)	0 (0)	0.11	2 (6)	1 (1)	0 (0)	0.57
Substance use	**Smoked in pregnancy** n (%)	4 (4)	9 (7)	2 (3)	0.39	3 (1)	4 (6)	0 (0)	0.085
	Alcohol in pregnancy: n (%)	3 (3)	9 (7)	3 (4)	0.38	1 (0)	6 (8)	0 (0)	<0.001
HIV disease	**WHO stage** n (%)	N=81	N=109	N=66		N=186	N=66	N=18	
	stage 1	63 (78)	57 (52)	29 (44)		145 (78)	32 (48)	3 (17)	
	stage 2	11 (14)	17 (16)	5 (8)		25 (13)	8 (12)	2 (11)	
	stage 3	6 (7)	27 (25)	22 (33)		14 (8)	18 (27)	11 (61)	
	stage 4	1 (1)	8 (7)	10 (15)	<0.001	2 (1)	8 (12)	2 (11)	<0.001
	Immunological status cells/mm^3 n (%)	N=157	N=254	N=142		N=290	N=116	N=21	
	0-50	12 (8)	26 (10)	21 (15)		19 (7)	5 (4)	4 (19)	
	50-100	25 (16)	40 (16)	26 (18)		43 (15)	13 (11)	6 (29)	
	100-150	32 (20)	55 (22)	35 (25)		75 (26)	29 (25)	4 (19)	
	150-200	42 (27)	79 (31)	35 (25)		89 (31)	42 (36)	5 (24)	
	200-250	46 (29	54 (21)	25 (18)	0.20	64 (22)	27 (23)	2 (10)	0.12
	median CD4 cell count	164.0	155.5	138.0		154.0	159.5	109.0	
	IQR	*103-203*	*97-193*	*76-188*	0.034	*107-196*	*130-196*	*74-164*	0.012
Health status	**Hypertension in pregnancy** n (%)	8 (8)	23 (12)	10 (9)	0.59	12 (5)	15 (16)	0 (0)	0.003
	Diabetes history n (%)	1 (1)	0 (0)	0 (0)	0.22	1 (0)	1 (1)	0 (0)	0.76
	Haemoglobin (Hb)	N=97	N=133	N=82		N=185	N=86	N=15	
	Hb<11gm/dl, n (%)	38 (39)	58 (43)	33 (40)	0.78	88 (48)	42 (49)	10 (67)	0.36
	median Hb gm/dl	11.2	11.2	11.5		11.0	11.1	10.2	
	IQR	*10.1-11.9*	*10.2-12.2*	*9.5-12.4*	0.63	*9.9-11.7*	*10.0-11.8*	*8.6-12.0*	0.38
	Syphilis serology n positive RPR (%)	5 (5)	4 (4)	2 (3)	0.84	8 (3)	3 (3)	0 (0)	0.78
	TB history n (%)	1 (10)	25 (14)	25 (28)	0.01	0 (0)	12 (15)	1 (17)	0.91
Reproductive health	**Gravidity** n (%)	N=108	N=196	N=109		N=237	N=100	N=17	
	1	15 (14)	19 (10)	17 (16)		43 (18)	9 (9)	5 (29)	
	2	37 (34)	71 (36)	34 (31)		94 (40)	40 (40)	6 (35)	
	3	37 (34)	61 (31)	33 (30)		63 (27)	31 (31)	4 (24)	
	≥4	19 (18)	45 (23)	25 (23)	0.66	37 (16)	20 (20)	2 (12)	0.29
	Previous miscarriage*: n (%)	22 (21)	36 (26)	12 (17)	0.34	23 (10)	11 (17)	4 (27)	0.059
	Previous preterm infant* n (%)	5 (5)	7 (8)	1 (2)	0.47	13 (6)	2 (5)	3 (23)	0.042

All women have a CD4 ≤250cells/mm^3; SD – standard deviation; *IQR* –interquartile range; RPR – rapid plasma reagin *in women with a previous pregnancy

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Table 3.1.3 Demographics and maternal health status in women attending HAART clinic at Rahima Moosa (RH) and Charlotte Maxeke Johannesburg Academic Hospital (JH)

Variable category	Variables	HAART-unexposed (A) N=233	HAART-exposed RM (B) N=690	HAART exposed JH (C) N=707	*P* value (B vs. C)
Demographics	**Maternal age**	N=180	N=681	N=691	
	mean years (SD)	28.9 (5.1)	30.2 (5.1)	30.4 (5.2)	0.53
	Race group n (%)	N=37	N=118	N=576	
	Black	34 (94)	108 (92)	572 (99)	
	mixed ancestry	2 (6)	8 (7)	2 (0)	
	Indian/White	0 (0)	2 (2)	2 (0)	<0.001
Substance use	**Smoked in pregnancy** n /(%)	6 (4)	14 (3)	14 (4)	0.36
	Alcohol use in pregnancy: n (%)	7 (5)	8 (2)	21 (6)	0.001
HIV disease	**WHO stage** n (%)	N=6	N=385	N=359	
	stage 1	3 (50)	281 (73)	165 (46)	
	stage 2	1 (17)	46 (12)	48 (13)	
	stage 3	1 (17)	46 (12)	114 (32)	
	stage 4	1 (17)	12 (3)	32 (9)	<0.001
	Immunological status CD4 cells/mm^3 n (%)	N=233	N=690	N=707	
	0-50	5 (2)	55 (8)	69 (10)	
	50-100	29 (12)	108 (16)	108 (15)	
	100-150	35 (15)	158 (23)	167 (24)	
	150-200	64 (27)	200 (29)	212 (30)	
	200-250	100 (43)	169 (24)	151 (21)	0.56
	mean CD4 cell count (SD)	176.0 (55.9)	147.8 (62.3)	144.4 (62.3)	0.31
Health status	**Hypertension in pregnancy** n (%)	18 (12)	33 (7)	60 (13)	0.005
	Diabetes history n (%)	1 (1)	3 (1)	0 (0)	0.08
	Haemoglobin (Hb) n (%)	N=100	N=427	N=485	
	Hb<11gm/dl	57 (57)	199 (47)	217 (45)	0.57
	Hb<7gm/dl	2 (2)	7 (2)	11 (2)	0.34
	median Hb (gm/dl)	10.7	11.0	11.2	
	IQR	*9.8-11.5*	*9.9-11.8*	*9.9-12.0*	*0.16*
	Syphilis serology n positive RPR (%)	3 (2)	19 (4)	16 (4)	0.89
Reproductive health	**Gravidity** n (%)	N=204	N=467	N=487	
	1	30 (15)	77 (16)	49 (10)	
	2	83 (41)	179 (38)	172 (35)	
	3	59 (29)	134 (29)	158 (32)	
	≥4	32 (16)	77 (16)	108 (22)	0.004
	Previous miscarriage*: n (%)	27 (18)	63 (14)	67 (22)	0.002
	Previous preterm infant* n (%)	16 (11)	26 (6)	13 (8)	0.28

All women have a CD4 ≤250cells/mm^3; SD – standard deviation; *IQR* –interquartile range; RPR – rapid plasma reagin
*in women with a previous pregnancy

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3.2.2 Substance use

Smoking

Information on smoking during pregnancy was available for 60% (140/233) of HAART-unexposed and 56% (777/1397) of HAART-exposed women. For both HAART-exposed and HAART-unexposed women, smoking rate was 4% (*P*=0.69).

Similar rates of smoking were found in RM and JH women (3% vs. 4%, *P*=0.36).

Women exposed to early and late HAART had similar rates of smoking (5% vs. 2%, *P*=0.085) as did women exposed to different HAART regimens.

Alcohol and illicit substance use

Information on alcohol or illicit substance use during pregnancy was available for 62% (140/233) of HAART-unexposed and 56% (782/1397) of HAART-exposed women. No women reported use of illicit substances. HAART-exposed and HAART-unexposed women had similar rates of alcohol use (4% vs. 5%, *P*=0.51).

A higher rate of alcohol use was reported at JH than RM (6% vs. 2%, *P*=0.001).

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Early and late HAART-exposed women reported similar rates of alcohol use (5% vs. 2%, *P*=0.085). In early HAART-exposed women, no regimen had a significant association with alcohol use (*P*=0.38). In late HAART-exposed women, NVP-based HAART was associated with a higher rate of alcohol use (8%) than PI-based (0%) and EFV-based (0%) regimens (*P*<0.001).

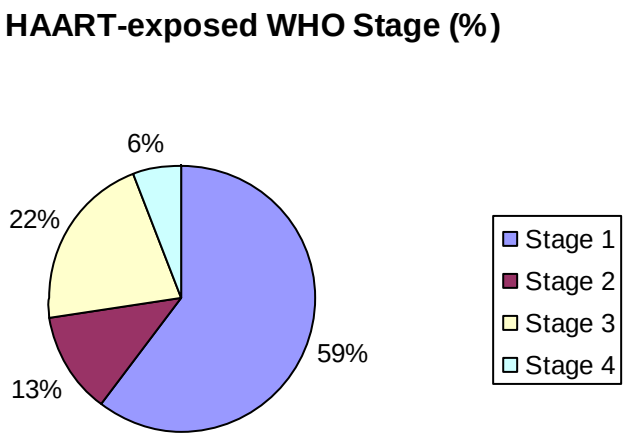
3.2.3 HIV Disease

WHO clinical stage

WHO clinical stage of HIV was unavailable for the majority of HAART-unexposed women. In the HAART-exposed group, 53% (744/1397) of women had a documented WHO clinical stage. The majority of women, 60%, were WHO clinical stage 1 with 13%, 22% and 6% in WHO clinical stages 2, 3 and 4 respectively.

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Figure 3.2.2 WHO clinical stages in HAART-exposed women

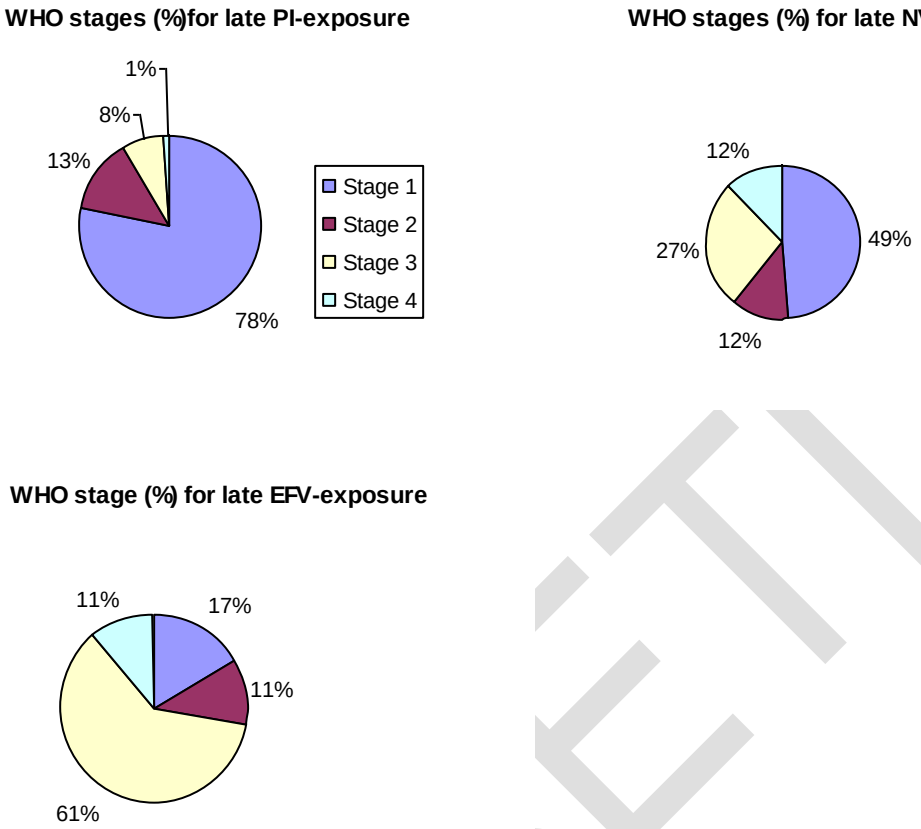


Among RM HAART-exposed women, a higher rate had WHO clinical stage 1 disease than among JH women (73% vs. 46%, *P*<0.001). JH women had a higher rate of stage 3 disease than RM women (32% vs. 12%, *P*<0.001).

Women exposed to early and late HAART had similar rates of WHO clinical stages 1 through 4. For both early and late HAART groups, PI-exposed women had a higher rate of stage 1 disease than NVP-exposed and EFV-exposed women (*P*<0.001). Among women exposed to late HAART, more EFV-exposed women were stage 3 disease compared to NVP-exposed and PI-exposed women (61% [11/18] vs. 27% [18/66] and 8% [14/186], *P*<0.001).

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Figure 3.2.3 WHO clinical stages for late HAART exposure according to regimen



Immunological status

The immunological status in the form of a CD4 cell count was known for all women included in the study. The median CD4 cell count for the HAART-unexposed women was higher than that of HAART-exposed (191cells/mm^3 [IQR136-220] vs.154cells/mm^3 [IQR101-195], *P*<0.001).

Mean CD4 cell count of was similar between RM and JH women (147.8cells/mm^3 vs. 144.4cells/mm^3, *P*=0.31) and women exposed to early HAART had a similar mean CD4 cell count to those exposed to late HAART (141.8cells/mm^3 vs. 149.9cells/mm^3, *P*=0.12).

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Among the early HAART group, EFV-exposed women had the lowest median CD4 cell count, followed by NVP-exposed and then PI-exposed women (138cells/mm^{3}vs. 155.5cells/mm^3 vs. 164cells/mm^3, *P*=0.034). Among the late HAART group, EFV-exposed women had the lowest median CD4 cell count, followed by PI-exposed and then NVP-exposed women (109cells/mm^3 vs. 154cells/mm^3 vs. 159cells/mm^3, *P*=0.012). Median CD4 cell counts for PI-exposed and NVP-exposed women were similar (*P*=0.35).

3.2.4 Health status

Hypertension

Information on the presence of hypertension requiring medication was available for 62% (145/233) of HAART-unexposed and 66% (929/1397) of HAART-exposed women. Hypertension was present in 12% of HAART-unexposed and 10 % of HAART-exposed women (*P*=0.38).

More JH than RM HAART-exposed women were hypertensive (13% vs. 7% *P*= 0.005).

Similar rates of hypertension were found in early and late HAART-exposed women (10% vs. 8%, *P*=0.32). For early HAART-exposed women, no regimen was associated with significantly higher rates of hypertension. For Late HAART-exposed women, NVP-based HAART was associated with a higher rate of hypertension than PI or EFV-based HAART (16% vs. 5% and 0%, *P*=0.003).

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Diabetes

Information on diabetes requiring medication was available for 63% (147/233) of HAART-unexposed and 67% (932/1397) of HAART-exposed women. Few women were identified as being diabetic – one HAART-unexposed and three HAART-exposed women and all these were from RM hospital.

Of HAART-exposed diabetics, one started HAART early (on PI-based HAART) and two started HAART late (one on PI-based and one on NVP-based HAART).

Anaemia

Anaemia was defined as haemoglobin less than 11gm/dl. Haemoglobin value during pregnancy was available for 43% (100/233) of HAART-unexposed and 65% (912/1397) of HAART-exposed women. High rates of anaemia were found in all groups with 57% of HAART-unexposed and 46% of HAART-exposed women having haemoglobin values of less than 11gm/dl (*P*=0.03) and 2% of women in both groups having haemoglobin values of less than 7gm/dl. Mean haemoglobin values for HAART-unexposed and exposed women were 10.6gm/dl (SD 1.5) and 10.9gm/dl (SD 1.6) respectively (*P*=0.06)

The rates of anaemia for RM and JH women were similar (47% vs.45%, *P*=0.57).

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Of women exposed to early and late HAART, 41% and 49% were anaemic respectively (*P*=0.062). Rates of anaemia did not differ across the different regimens in the early (*P*=0.78) and late (*P*=0.36) groups.

Syphilis

Syphilis serology (Rapid Plasma Reagin [RPR]) results were available for 59% (137/233) of HAART-unexposed and 62% (864/1397) of HAART-exposed women. Among HAART-unexposed and HAART-exposed groups, 3 (2%) and 35 (4%) were found to be RPR positive respectively (*P*=0.29).

Positive RPR rates were similar in RM and JH women (both 4% [*P*=0.89] as well as women exposed to early and late HAART (4% vs. 3%, *P*=0.60) and across all treatment regimens.

Tuberculosis

Information on tuberculosis (TB) was only available for HAART-exposed JH women and among these only 33% (466/1397) had documented TB information. Of these women, 17% (80/466) had a history of TB.

Among the early HAART group, EFV-exposed women had a higher rate of positive TB history than NVP-exposed or PI-exposed women (28% [25/88] vs. 14% [25/183] and 10% [1/10], *P*=0.01). In the late HAART group, 0% (0/1), 15% (12/78) and 17% (1/6) of women

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exposed to PI-based, NVP-based and EFV-based HAART respectively had a history of TB (*P*=0.91).

3.2.5 Reproductive Health

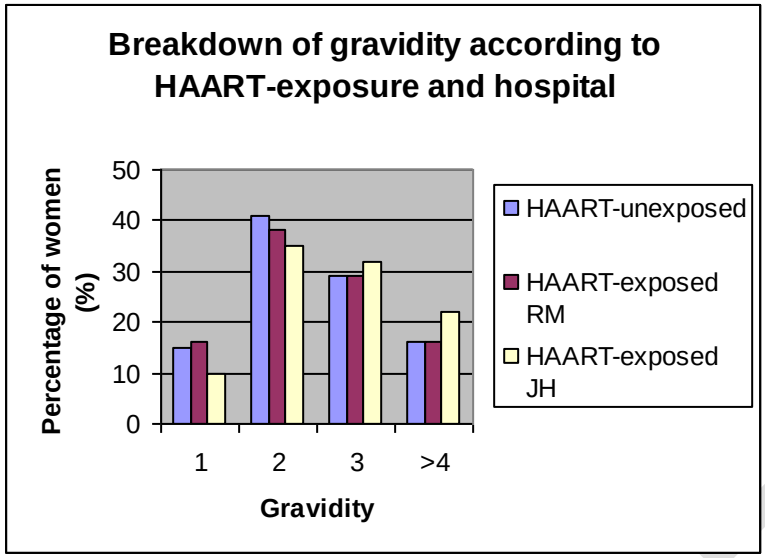
Gravidity

Information on gravidity was available for 88% (204/233) of HAART-unexposed and 68% (954/1397) of HAART-exposed women. These groups did not differ in terms of gravidity with the majority of women on their second or third pregnancy – 41% and 29% of HAART-unexposed and 37% and 31% of HAART-exposed respectively (*P*=0.50). Only 15% of HAART-unexposed and 13% of HAART-exposed women were primigravida. Both HAART-unexposed and HAART-exposed women had a median gravidity of 2 (IQR 2-3) (*P*=0.13).

HAART-exposed women at RM had a more primigravida women than JH (16% vs. 10%) and fewer women with a gravidity of 4 or more than JH (16% vs. 22%, *P*=0.004).

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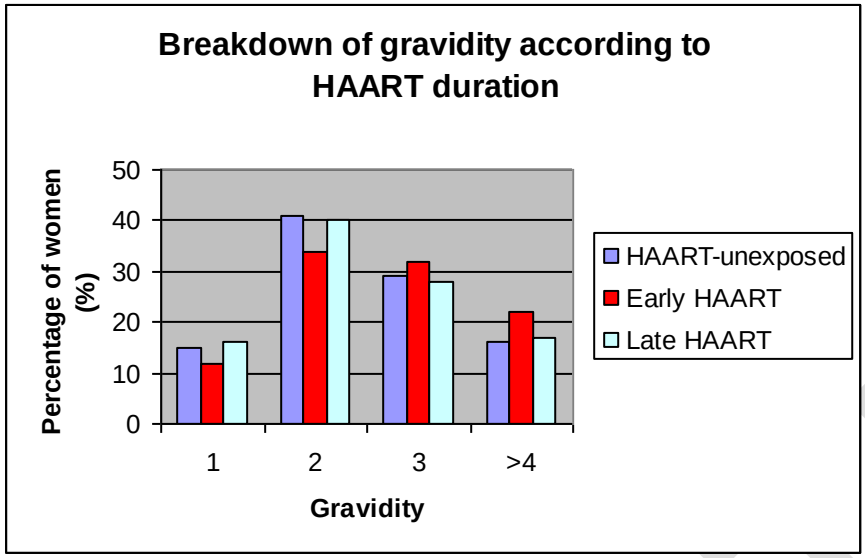
Figure 3.2.4 Breakdown of gravidity according to HAART-exposure and hospital



Among the HAART-exposed group, for both early and late HAART, most women were on their second or third pregnancies. Women exposed to early HAART were more likely to be on their third pregnancy (median gravidity of 3) versus women exposed to late HAART who were more likely to be on their second pregnancy (median gravidity of 2) (*P*=0.01). Only 12% and 16% of women were primigravida in the early and late HAART-exposed groups respectively.

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Figure 3.2.5 Breakdown of gravidity according to HAART duration



The breakdown for gravidity within early and late HAART groups according to regimens did not differ significantly (see table 3.1.2).

Previous miscarriage

Previous miscarriage rate was assessed for all women with a previous pregnancy. The rates of previous miscarriage were available for 84% (146/174) of HAART-unexposed and 93% (766/828) of HAART-exposed women and these did not differ significantly (18% vs. 17%, *P*=0.66).

There were more previous miscarriages in the JH HAART-exposed group (22%) compared to the RM HAART-exposed group (14%) (*P*=0.002).

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Previous miscarriages were more common in women exposed to early HAART than late HAART (22% vs.12%, *P*=0.001). Rates of previous miscarriages were similar for all regimen groups.

Previous preterm birth

Previous preterm birth rate was assessed for all women with a previous pregnancy. This was available for 85% (148/174) of HAART-unexposed and 75% (621/828) of HAART-exposed women who were known to have had a previous pregnancy. HAART-unexposed and HAART-exposed women had a previous preterm birth rate of 11% and 6% respectively (*P*=0.055).

RM and JH HAART-exposed women had similar previous preterm birth rates of 6% and 8% respectively (*P*=0.28).

Both early and late HAART women had previous preterm rates of 6% (*P*=0.71). Women exposed to early HAART had similar previous preterm rates across all regimen types. Women exposed to EFV-based late HAART had higher previous preterm rates than those exposed to PI-based or NVP-based late HAART (23% vs. 6% or 5%, *P*=0.042).

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Summary: demographics and maternal health status

Table 3.1.4 Summary of demographic and maternal health status variables

Variables showing no difference across groups marked with X
Variables showing a difference are marked with D

Variable	HAART-exposed vs. HAART-unexposed	Early HAART vs. late HAART	RM vs. JH	PI vs. NVP. vs. EFV in early HAART	PI vs. NVP vs. EFV in late HAART
Age	D	X	X	X	X
Race	X	D	D	X	X
Smoking	X	X	X	X	X
Alcohol	X	X	D	X	D
WHO stage	X	X	D	D	D
CD4 cell count group	D	X	X	X	X
CD4 cell count median	D	X	X	D	D
Hypertension	X	X	D	X	D
Diabetes	X	X	D	X	X
Anaemia	D	X	X	X	X
Syphilis	X	X	X	X	X
Gravidity	X	X	D	X	X
Previous miscarriage	X	D	D	X	X
Previous preterm	X	X	X	X	D

HAART-highly active antiretroviral therapy; RM – Rahima Moosa Mother and Child Hospital; JH – Charlotte Maxeke Johannesburg Academic Hospital; PI- protease inhibitor (exposure); NVP – nevirapine (exposure); EFV –efavirenz (exposure)

Most women in the study were black, aged between 25 and 34 and experiencing their second or third pregnancy. HAART exposed women were older, had lower CD4 cell counts, and higher haemoglobin values than HAART-unexposed women. Women exposed to early HAART had more previous miscarriages than those exposed to late HAART. JH women had higher gravidity, more advanced HIV WHO clinical stage, increased alcohol use, increased likelihood of hypertension and more previous miscarriages than RM women. Women exposed to EFV-based HAART had the lowest median CD4 cell counts, the most clinically advanced HIV and were more likely to have a history of TB. Women exposed to late NVP-based HAART had higher alcohol use than those exposed to other regimens.

3.3 PERINATAL CHARACTERISTICS AND INFANT OUTCOMES

3.3.1 Perinatal Characteristics

Pregnancy planning

Among the HAART-unexposed and exposed women, 52 (22%) and 321 (23%) were asked whether the current pregnancy was planned. More than two thirds of women in both groups had not planned the pregnancy – 71% (37/52) and 72% (232/321) in the two groups respectively.

Women exposed to early HAART had a lower rate of unplanned pregnancies than those exposed to late HAART but this was not significant (69% [97/141] vs. 79% [89/113], *P*=0.075).

Time to HAART initiation from first Antenatal visit

The amount of weeks from the first Antenatal visit to HAART initiation was available for 65% (903/1397) of HAART-exposed women. This was longest for EFV-based regimens followed by NVP-based and PI-based regimens (8.6 weeks [IQR4.3-17.9] vs. 5.2 weeks [IQR3.0-10.7] and 4.6 weeks [IQR2.3-8.0]).

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Table 3.2.1 Perinatal characteristics and infant outcomes in women exposed and unexposed to antiretroviral treatment, and by duration of exposure

Variable category	Variables	HAART-unexposed (A) N=233	HAART-exposed (B) N=1397	*P* value (A vs. B)	Early HAART-exposed (C) N=533	Late HAART-exposed (D) N=427	*P* value (C vs. D)
Pregnancy and Delivery	**Time taking HAART until delivery**		N=921		N=412	N=416	
	median weeks		9.7		18.4	5.8	
	IQR		*5.0-17.6*		*12.1-42.6*	*3.3-8.5*	<0.001
	Mode of delivery n (%)	N=188	N=1026		N=412	N=410	
	vaginal birth	138 (73)	734 (72)		295 (72)	296 (72)	
	c/s emergency	36 (19)	179 (17)		68 (17)	69 (17)	
	c/s elective	14 (7)	113 (11)	0.32	49 (12)	45 (11)	0.92
Infant Outcomes	**Infant gender** n (%)	N=227	N=994		N=412	N=409	
	female	111 (49)	496 (50)	0.79	210 (51)	205 (50)	0.81
	Gestation n (%)	N=147	N=946		N=389	N=427	
	extremely premature	6 (4)	58 (6)		40 (10)	3 (1)	
	preterm	1 (1)	80 (8)		41 (11)	18 (4)	
	term/postdates	140 (95)	808 (85)	0.002	308 (79)	406 (95)	<0.001
	Birth weight (kg) n (%)	N=224	N=1004		N=388	N=407	
	mean (SD)	2.8 (0.6)	2.9 (0.6)	0.008	2.9 (0.6)	2.9 (0.5)	0.39
	0.75-1.49	10 (4)	16 (2)		8 (2)	2 (0)	
	1.5-2.49	50 (22)	199 (20)		82 (21)	74 (18)	
	>2.5	164 (73)	789 (79)	0.015	298 (77)	331 (81)	0.071
	Birth weight – gestation n (%)	N=138	N=792		N=312	N=400	
	AGA	77 (56)	541 (68)		232 (74)	245 (61)	
	SGA	59 (43)	214 (27)		57 (18)	147 (37)	
	LGA	2 (1)	37 (5)	<0.001	23 (7)	8 (2)	<0.001
	Infant head circumference (cm)	N=138	N=801		N=312	N=332	.
	mean (SD)	33.7 (2.5)	34.1 (2.2)	0.034	34.0 (2.4)	34.3 (2.1)	0.20
	Infant HIV status n (%)	N=191	N=828		N=350	N=316	
	HIV PCR positive	37 (19)	45 (5)	<0.001	8 (2)	31 (10)	<0.001

IQR – interquartile range; PI- protease inhibitor, NVP – nevirapine; EFV – efavirenz; C/s – caesarean section; SD – standard deviation; AGA – appropriate for gestational age; SGA – small for gestational age; LGA – large for gestational age; PCR –polymerase chain reaction

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Table 3.2.2 Perinatal characteristics and infant outcomes in women receiving different antiretroviral regimens in pregnancy

Variable category	Variables	Early HAART-exposed			*P*	Late HAART-exposed			*P*
		PI-based HAART	NVP-based HAART	EFV-based HAART		PI-based HAART	NVP-based HAART	EFV-based HAART	
Pregnancy and Delivery	**Time taking HAART until delivery**	N=139	N=192	N=81		N=290	N=107	N=19	
	median weeks	17.1	15.6	62.7		6.1	5.1	5.2	
	IQR	*13.7-23.1*	*10.7-25.8*	*33.1-86.4*	<0.001	*3.3-8.7*	*3.0-7.8*	*3.9-9.4*	0.38
	Mode of delivery: n (%)	N=135	N=181	N=96		N=278	N=113	N=19	
	vaginal birth	108 (80)	123 (68)	64 (67)		220 (79)	65 (58)	11 (58)	
	c/s emergency	19 (14)	27 (15)	22 (23)		38 (14)	26 (23)	5 (26)	
	c/s elective	8 (6)	31 (17)	10 (10)	0.009	20 (7)	22 (19)	3 (16)	<0.001
Infant Outcomes	**Infant gender**: n (%)	N=134	N=179	N=99		N=280	N=109	N=20	
	female	64 (48)	95 (53)	51 (52)	0.64	138 (49)	55 (50)	12 (60)	0.65
	Gestation: n (%)	N=131	N=167	N=91		N=290	N=116	N=21	
	extremely premature	13 (10)	15 (9)	12 (13)		0 (0)	3 (3)	0 (0)	
	preterm	6 (5)	25 (15)	10 (11)		9 (3)	8 (7)	1 (5)	
	term/postdates	112 (86)	127 (76)	69 (76)	0.048	281 (97)	105 (91)	20 (95)	0.024
	Birth weight (kg): n (%)	N=135	N=158	N=95		N=284	N=103	N=20	
	mean (SD)	3.0 (0.6)	2.9 (0.5)	2.7 (0.6)	0.002	2.9 (0.5)	2.9 (0.5)	2.8 (0.5)	0.59
	0.75-1.49	5 (4)	0 (0)	3 (3)		2 (1)	0 (0)	0 (0)	
	1.5-2.49	18 (13)	31 (20)	33 (35)		46 (16)	23 (22)	5 (25)	
	>2.5	112 (83)	127 (80)	59 (62)	<0.001	236 (83)	80 (78)	15 (75)	0.50
	Birth weight – gestation n (%)	N=123	N=128	N=61		N=280	N=101	N=19	
	AGA	83 (67)	110 (86)	39 (64)		153 (55)	79 (78)	13 (61)	
	SGA	26 (21)	13 (10)	18 (30)		121 (43)	20 (20)	6 (32)	
	LGA	14 (11)	5 (4)	4 (7)	0.001	6 (2)	2 (2)	0 (0)	0.001
	Infant head circumference (cm):	N=91	N=141	N=80		N=218	N=98	N=16	
	mean (SD)	33.9 (2.4)	34.5 (2.6)	33.5 (1.9)	0.006	34.1 (2.0)	34.6 (2.3)	33.8 (2.0)	0.10
	Infant HIV status: n (%)	N=106	N=156	N=88		N=214	N=87	N=15	
	HIV PCR positive	1 (1)	6 (4)	1 (1)	0.22	17 (8)	13 (15)	1 (7)	0.17

IQR – interquartile range; PI- protease inhibitor, NVP – nevirapine; EFV – efavirenz; C/s – caesarean section; SD – standard deviation;
AGA – appropriate for gestational age; SGA – small for gestational age; LGA – large for gestational age; PCR –polymerase chain reaction

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Table 3.2.3 Perinatal characteristics and infant outcomes in women attending HAART clinics at Rahima Moosa (RM) and Charlotte Maxeke Johannesburg Academic Hospital (JH)

Variable Category	Variable	RM	JH	*P value*
HAART	**HAART duration in pregnancy** (median weeks)			
	early HAART (median weeks)	17.9	18.9	
	IQR	*14.7-26.6*	*10.9-58.1*	0.58
	late HAART (median weeks)	6	5.1	
	IQR	*3.2-8.7*	*3.1-7.9*	0.24
	HAART Regimen n (%)	N=690	N=707	
	PI-based	589 (85)	21 (3)	
	NVP-based	55 (8)	525 (74)	
	EFV-based	46 (7)	161 (23)	<0.001
Delivery	**Mode of delivery** n (%)	N=565	N=461	
	vaginal birth	431 (76)	303 (66)	
	c/s emergency	93 (16)	86 (19)	
	c/s elective	41 (7)	72 (16)	<0.001
Infant Outcomes	**Infant gender** n (%)			
	female	272 (49)	224 (51)	0.38
	Gestation n (%)	N=553	N=393	
	extremely premature	19 (3)	39 (10)	
	preterm	28 (5)	52 (13)	
	term/postdates	506 (92)	302 (77)	<0.001
	Birth weight (kg) n (%)	N=571	N=432	
	mean (SD)	2.9 (0.6)	2.9 (0.6)	
	0.75-1.49	12 (2)	4 (1)	
	1.5-2.49	109 (19)	90 (21)	
	>2.5	451 (79)	338 (78)	0.28
	Birth weight – gestation n (%)	N=505	N=287	
	AGA	292 (58)	249 (87)	
	SGA	187 (37)	27 (9)	
	LGA	26 (5)	11 (4)	<0.001
	Infant head circumference (cm):			
	mean (SD)	33.9 (2.1)	34.3 (2.2)	
	median	34	34	
	IQR	*33-35*	*33-35*	0.014
	Infant HIV status: n (%)			
	HIV PCR positive	25 (6)	20 (5)	0.66

early HAART – HAART initiated before 28 weeks of pregnancy; late HAART – HAART initiated at or after 28 weeks of pregnancy; IQR – interquartile range; PI- protease inhibitor, NVP – nevirapine; EFV – efavirenz; c/s – caesarean section; SD – standard deviation; AGA – appropriate for gestational age; SGA – small for gestational age; LGA – large for gestational age; PCR –polymerase chain reaction

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Duration of HAART

(See tables 3.2.1, 3.2.2 and 3.2.3)

Duration of HAART from initiation to delivery was available for 66% (921/1397) of women exposed to HAART. The median weeks on HAART for women who received early and late HAART was 5.8 weeks (IQR3.3-8.5) and 18.4 weeks (IQR12.1-42.6) respectively (*P*<0.001).

Women from RM and JH had similar median durations of early HAART (17.9 vs. 18.9 weeks, *P*=0.58) and late HAART (6.0 vs. 5.1 weeks, *P*=0.24).

Among the early HAART-exposed group, the median weeks on HAART was longer for EFV-exposed than PI-exposed or NVP-exposed women (62.7 [IQR33.1-86.4] vs. 17.1 [IQR13.7-23.1] and 15.6 [IQR10.7-25.8], *P*<0.001).

Among the late HAART-exposed group, the median weeks on HAART was similar for PI-based, NVP-based and EFV-based regimens (6.1 [IQR3.3-8.7] vs. 5.1 [IQR3.0-7.8] vs. 5.2 [IQR3.9-9.4], *P*=0.38).

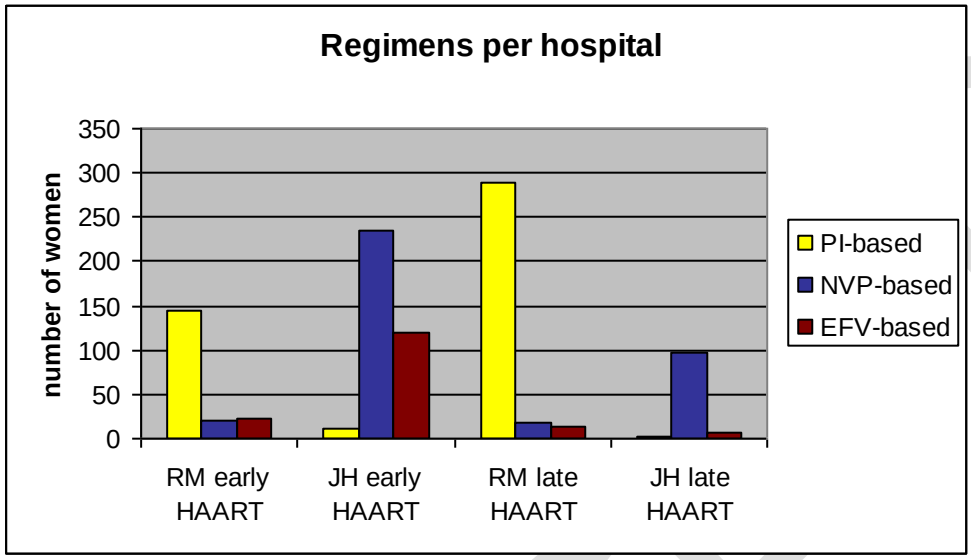
Site of delivery – Regimen preference for study hospitals

At RM hospital, the main regimen used was PI-based - 85% (589/690) of all HAART, 77% (145/188) of early and 90% (288/321) of late HAART. At JH hospital the main regimen used was NVP-based - 74% (525/707) of all HAART, 64% (234/365) of early and 92% (97/106) of

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late HAART. More JH women used EFV-based HAART than RM (23% vs.7%, *P*<0.001) particularly in the early HAART-exposed women.

Figure 3.3.1 Regimens per hospital



Mode of delivery

Mode of delivery was known for 81% (188/233) of HAART-unexposed and 73% (1026/1397) of HAART-exposed women. Vaginal birth occurred most commonly among both HAART-unexposed and HAART-exposed (72% [734/1026] vs. 73% [138/188], *P*=0.32). Women exposed to early and late HAART were equally likely to have a vaginal birth (72% [295/412] vs. 72% [296/410], *P*=0.92).

Of women exposed to early HAART, PI-exposed women had more vaginal births than those with NVP and EFV-exposure (80% [108/135]) vs. 68% [123/181] and 67% [64/96], *P*=0.009).

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Of women exposed to late HAART, PI-exposed women also had more vaginal births than their NVP-exposed and EFV-exposed counterparts (79% [220/278] vs. 58% [65/113] vs. 58% [11/19], *P*<0.001).

3.3.2 Infant Outcomes

Infant gender

Infant gender was recorded for 97% (227/233) of HAART-unexposed and 71% (994/1397) of HAART-exposed infants. Roughly half of all infants were female – 49% of HAART-unexposed, 50% of HAART-exposed, 51% of early HAART-exposed, and 50% of late HAART-exposed. The male/female split was not different across the three regimen groups.

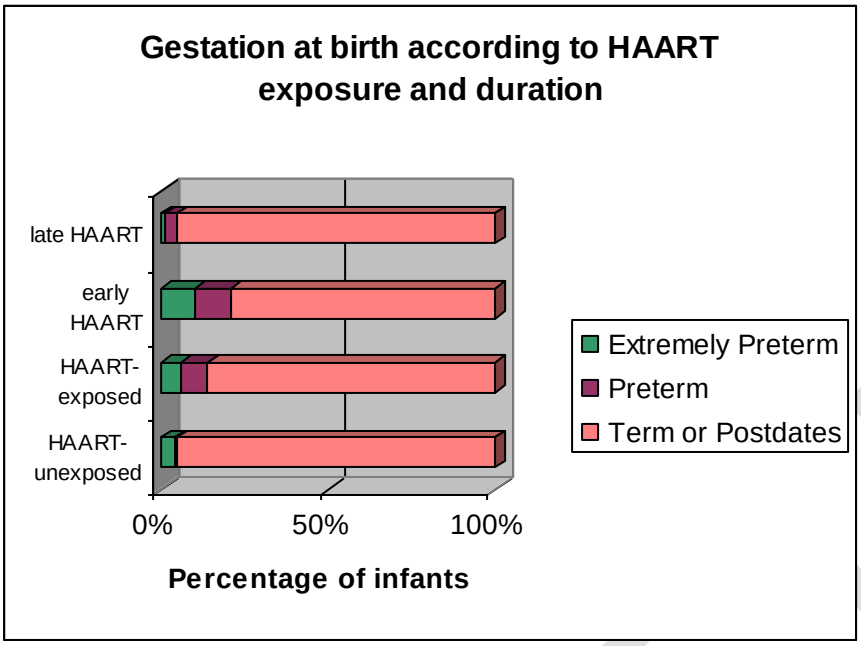
Gestation

Gestation at birth was known for 63% (147/233) of HAART-unexposed and 68% (946/1397) of HAART-exposed infants.

Preterm birth rates were higher in HAART-exposed infants than HAART-unexposed infants (15% [138/946] vs. 5% [7/147], *P*=0.002). More infants exposed to early HAART were born preterm than those with late HAART exposure (21% [81/389] vs. 5% [21/427], *P*<0.001).

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Figure 3.3.2 Gestation at birth according to HAART exposure and duration

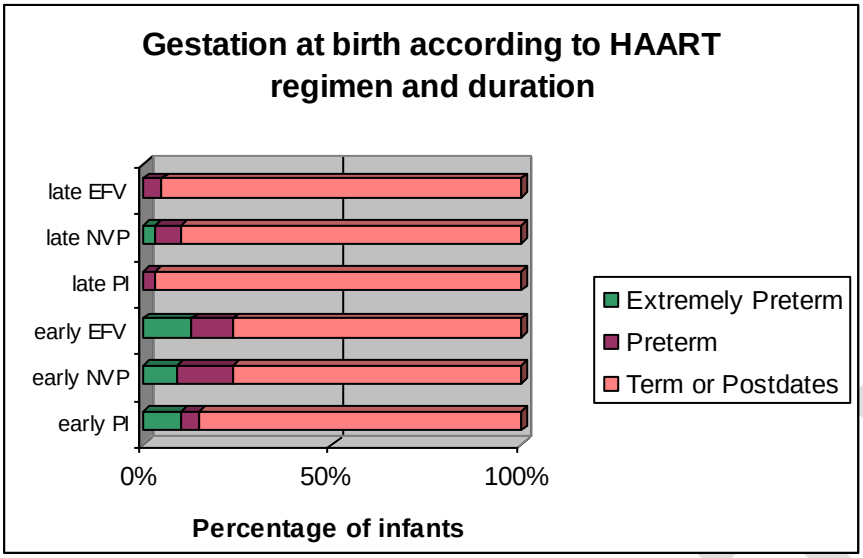


Among early HAART-exposed infants, NVP and EFV-exposure were linked to higher rates of preterm births than PI-exposure (24% [40/167] and 24% [22/91] vs. 15% [19/131], *P*=0.048).

Among late HAART-exposed infants, preterm birth rates were highest for NVP-based followed by EFV-based and then PI-based regimens (9% [11/116] vs. 5% [1/21] vs. 3% [9/290], *P*=0.024).

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Figure 3.3.3 Gestation at birth according to HAART regimen and duration



Similar rates of extremely premature infants were born to HAART-unexposed and HAART-exposed women (4% [6/147] vs. 6% [58/946], *P*=0.97). More early HAART-exposed than late HAART-exposed infants were extremely premature (10% [40/389] vs. 1% [3/427], *P*<0.001).

Among early HAART-exposed infants the rate of extremely premature infants was similar for PI-based, NVP-based and EFV-based regimens (10% [13/131] vs. 9% [15/167] vs. 13% [12/91], *P*=0.56). In the late HAART-exposed group, three infants were born extremely premature after exposure to NVP-based regimens and none were born extremely premature after PI or EFV exposure (3% [3/116] vs. 0% [0/290] vs. 0% [0/21], *P*=0.017).

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Birth Weight

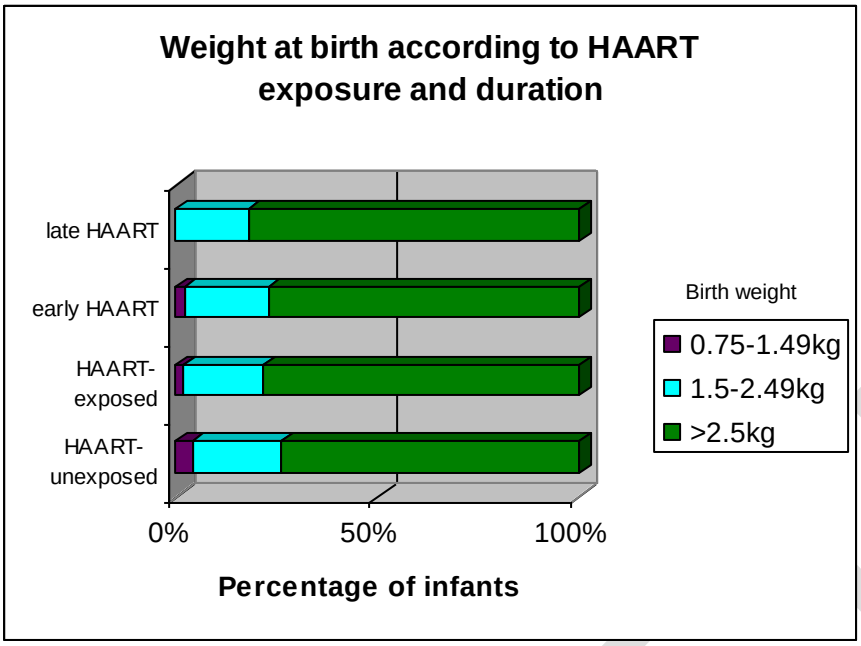
Low birth weight

Birth weight was known for 96% (224/233) of HAART-unexposed and 72% (1003/1397) of HAART-exposed infants. The mean birth weight for the cohort was 2.88kg, with just less than a quarter of infants LBW (22.4% [275/1228]). Among infants with known HIV status, HIV-positive infants had a higher rate of LBW than HIV negative infants (33% [24/73] vs. 22% [173/804], P=0.04).

The mean birth weight for HAART-unexposed infants was 0.1kg less than those exposed to HAART (2.8kg [SD 0.6] vs. 2.9kg [SD 0.6], *P*=0.008). Similarly, more HAART-unexposed infants, were low birth weight (LBW) compared to HAART-exposed infants (27% [60/224] vs. 21% [215/1003], *P*=0.081). Among the HAART-exposed group, a similar rate of LBW was found in early HAART-exposed infants versus late HAART-exposed infants (23% [90/388] vs. 19% [76/407], *P*=0.12).

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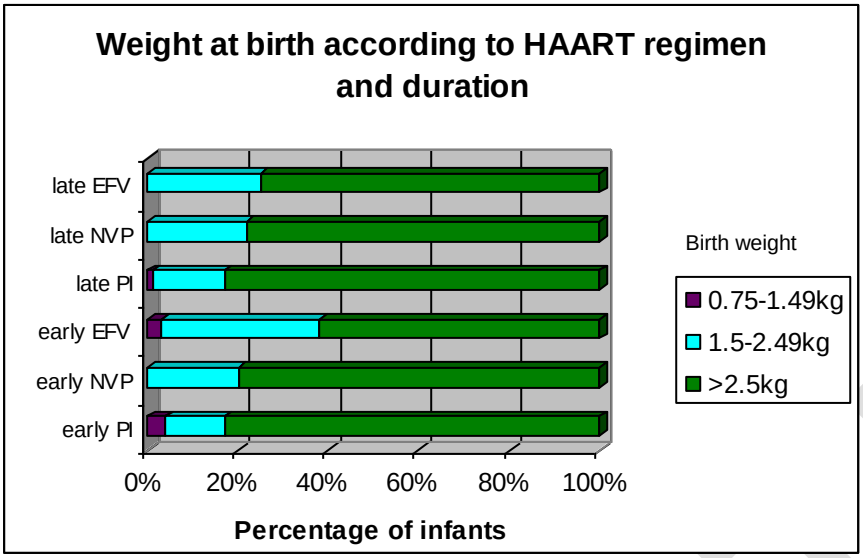
Figure 3.3.4 Weight at birth according to HAART exposure and duration



Among early HAART-exposure, women on EFV-based regimens had the highest rate of LBW followed by NVP-based and then PI-based regimens (38% [36/95] 20% [31/158] 17% [23/135], *P*<0.001). Among late HAART-exposure, women on EFV based regimens had the highest rate of LBW followed by NVP-based and then PI-based regimen (25% [5/20] vs. 22% [23/103] vs.17% [48/284], *P=0.36*).

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Figure 3.3.5 Weight at birth according to HAART regimen and duration



Very low birth weight

Overall, only 26 (2%) infants were very low birth weight (VLBW). Table 3.3.1 summarises the maternal and infant characteristics of the 26 VLBW infants.

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Table 3.3.1: Maternal and infant characteristics of very low birth weight infants.

CD4	Age	Site	WHO stage	Gravidity	Known risk factors	PMTCT	Weeks on HAART	Infant gender	Mode of delivery	Birth weight (kg)	Gestation (weeks)	weight vs. gestation	Infant PCR result
18	39	RM		3	PP	PI HAART	3	Male	em. c/s	1.48	30	AGA	Negative
51	31	JH				NVPHAART	unknown		NVD	1.21	27	AGA	
51	33	RM		3	Hypertension	PI HAART	11	Male	NVD	0.65	30	SGA	
51	31	RM	1	2		PI HAART	19	Male	NVD	1.45	35	SGA	Negative
57	34	JH	1	4		EFV HAART	unknown	Male	em. c/s	1.40			
96	38	RM	2	2	Hypertension	PI HAART	3	Male	NVD	1.26	29	AGA	Negative
99	36	RM		3		No HAART		Male	NVD	1.40	35	SGA	Negative
100	32	RM				PI HAART	73	Female	NVD	1.10	27	AGA	Negative
110	27	RM	1	2	PMc	PI HAART	1	Female	NVD	1.02	27	AGA	Negative
111	19	RM		1		No HAART		Male	em. c/s	1.10	28	AGA	Negative
128	27	RM	1	1		PI HAART	13	Male	NVD	1.42			
136	35	RM		3	PMc, PP	No HAART		Male	NVD	1.03	30	AGA	
149	32	JH	1	3		EFV HAART	145	Female	NVD	1.40	30	AGA	
149		RM		3		No HAART		Female	em. c/s	1.20			Negative
166	23	RM	1			PI HAART	unknown	Male	em. c/s	1.00	29	AGA	Negative
176		RM		2		No HAART		Male	NVD	1.39			Negative
189	35	RM				PI HAART	unknown	Female		1.43			Positive
200	27	RM		2	PMc, Alcohol, Smoking	No HAART		Female	em. c/s	1.10	27	AGA	Negative
208	31	RM		4		No HAART		Female	em. c/s	1.34	29	AGA	Negative
209	29	RM	3	1	Chorioamnionitis	PI HAART	unknown		NVD	1.25			
211		RM		2		No HAART		Male	NVD	1.27			Negative
220	31	RM	1			PI HAART	14	Female	NVD	1.24	31	AGA	
226	37	JH	1	4		EFV HAART	unknown	Female	em. c/s	1.02	28	AGA	Negative
239	24	RM				No HAART		Female		1.46			Negative
239	24	RM				No HAART		Female		1.26			Negative
248	32	RM		2		PI HAART	10	Male	NVD	1.30	32		

JH, Charlotte Maxeke Johannesburg Academic Hospital; RM, Rahima Moosa Mother and Child Hospital; PP, Previous preterm delivery,; PMc, Previous miscarriage; PI HAART, Protease inhibitor based antiretroviral regimen; EFV HAART, efavirenz based antiretroviral regimen; NVP HAART, nevirapine based antiretroviral regimen; No HAART, no HAART - single dose of nevirapine to mother and/or infant or PMTCT missed; em.c/s, emergency caesarean section; NVD, normal vaginal delivery; AGA' Appropriate for gestational age; SGA' small for gestational age; PCR, polymerase chain reaction test for HIV.

UNDER

The 26 VLBW infants had mothers aged between 19 and 39. Six women were 35 years or older. The mean maternal age of 30.7 years was not different to that of the rest of the cohort (30.0 years, *P*=0.05). Most VLBW pregnancies were managed at RM hospital (22/26) and more than a third of the women had a gravidity of 3 or more. CD4 cell counts of the mothers with VLBW infants ranged from 18 to 248cells/ mm^3. The mean CD4 cell count of the VLBW group did not differ from the rest of the women (147.6cells/mm^3 vs. 153.1cells/mm^3, *P*=0.65). Of the 26 infants, only seven (27%) had known risk factors for LBW, three of the women had a previous miscarriage, two had a previous preterm delivery and two where hypertensive. Two women had multiple risk factors for preterm birth.

More HAART-unexposed than HAART-exposed infants were VLBW (4% [10/224] vs. 2% [16/1004], *P*=0.01). Among the HAART-exposed women, eight early HAART-exposed and two late HAART-exposed infants were VLBW (2% [8/388] vs. 0% [2/407], *P*=0.05). The duration of HAART exposure varied considerably – between 1 and 145 weeks. Most of the HAART use was PI-based (80% [12/15]) but when early and late HAART were analysed separately, the rates of VLBW infants were similar for all regimens (*P*=0.58 and *P*=0.65 for early and late respectively).

The number of male and females in the group were almost equal (13 vs. 11). More than a third of the infants were born by emergency caesarean section.

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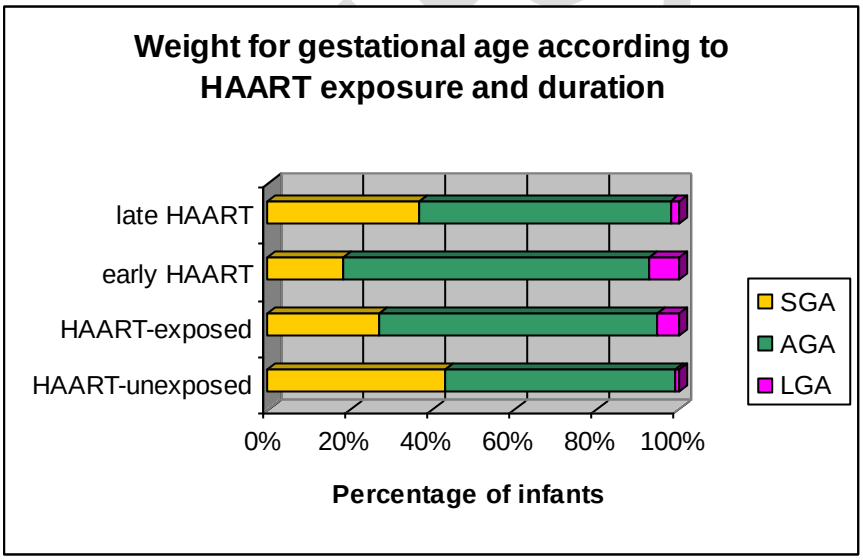
All infants were 35 weeks or less gestation at birth and most were classified as preterm with the lowest gestation being 27 weeks. Only three SGA infants were detected and only one VLBW infant had a documented positive HIV PCR.

Extremely low birth weight

Only one infant was classified as extremely LBW with a weight of 650g. This male infant was the result of the third pregnancy of a 33 year old. The mother had been on PI-based HAART for 11 weeks prior to developing pre-eclampsia resulting in a preterm birth at 30 weeks gestation.

Birth weight versus Gestation

Figure 3.3.6 Weight for gestational age according to HAART exposure and duration



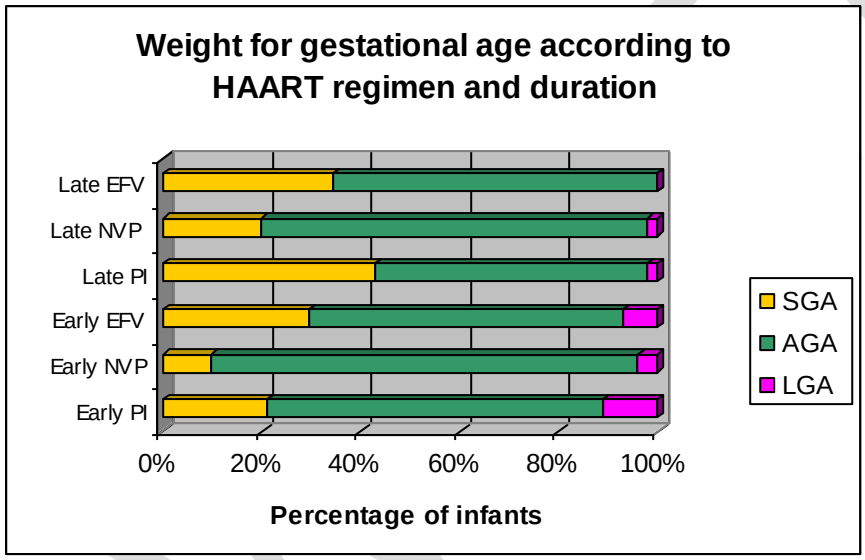
HAART-unexposed women had more SGA (small for gestational age) infants than HAART-exposed women (43% [59/138] vs. 27% [214/792], *P*<0.001).

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More SGA infants were born to HAART-exposed women at RM than at JH (37% [187/505] vs. 9% [27/287], *P*<0.001).

More SGA infants were born to women exposed to late versus early HAART (37% [147/400] vs.18% [57/312], *P*<0.001).

Figure 3.3.7 Weight for gestational age according to HAART regimen and duration



Among early HAART-exposure, EFV-exposure was associated with the most SGA infants followed by PI-exposure and then NVP-exposure (30% [18/61] vs. 21% [26/123] vs. 10% [13/128], *P*=0.001).

Among late HAART-exposure, PI-exposure was associated with more SGA infants followed by EFV-exposure and then NVP-exposure (43% [121/280] vs. 32% [6/19] vs. 20% [20/101], *P*=0.001)

Head circumference

The head circumference measurement at birth was available for 59% (138/233) of HAART-unexposed infants and 57% (801/1397) of HAART-exposed infants. The mean head circumference of HAART-exposed infants was 0.4cm more than HAART-unexposed infants. (34.1cm [SD2.2] vs. 33.7cm [SD2.5], *P*=0.034).

The head circumferences of Infants exposed to early and late HAART were similar (33.0cm [SD2.4] vs. 34.3cm [SD2.1], *P*=0.20).

Among the early HAART-exposed group, infants exposed to NVP had a bigger mean head circumference than those exposed to PIs or EFV (34.5cm [SD2.6] vs. 33.9cm [SD2.4] vs. 33.5cm [SD1.9], *P*=0.006).) In the late HAART-exposed group, mean head circumferences did not differ across PI, NVP or EFV-based regimens (34.1cm [SD2.0] vs. 34.6cm [SD2.3] vs. 33.8cm [SD2.0], *P*=0.10).

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Infant HIV status

Infant HIV status determined by DNA PCR at 6 weeks of age was available for 82% (191/233) of HAART-unexposed and 59% (828/1397) of HAART-exposed infants.

Rate of HIV positive tests among those tested was almost fourfold higher in the HAART-unexposed versus HAART-exposed infants (19% [37/191] vs. 5% [45/828], *P*<0.001). Infants exposed to late HAART were five times more likely to test HIV positive than those exposed to early HAART (10% [31/316] vs. 2% [8/350], *P*<0.001).

Among the early and late HAART-exposed groups, HIV positive testing rates were similar for PI, NVP and EFV exposure (1% [1/160] vs. 4% [6/154] vs. 1% [1/88], *P*=0.22 for early and 8% [17/214] vs.15% [17/214] vs. 7% [1/15], *P*=0.17 for late).

Summary: Perinatal characteristics and infant outcomes

The mean duration of HAART was 9.7 weeks; 18.4 weeks and 5.8 weeks for early and late HAART respectively. Women exposed to early EFV-based HAART had a longer median duration of HAART than other regimens. Most deliveries in the study were vaginal and women exposed to PI-based HAART were most likely to have vaginal deliveries. HAART-exposure was associated with increased preterm birth but PI-based HAART did not have an increased risk compared to other regimens. HAART-exposure was not associated with increased risk of LBW because HAART-unexposed women had increased risk of SGA

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infants. Infants exposed to HAART had higher head circumferences and lower HIV rates than HAART-unexposed infants.

Table 3.4.1 Association of demographic and maternal health variables with low birth weight (LBW) among HIV-negative infants

Variable Category	Variable	Low birth weight infants in all participants n/N (%LBW)	*P*	Low birth weight infants in HAART-unexposed n/N (%LBW)	*P*	Low birth weight infants in HAART-exposed group n/N (%LBW)	*P*	Low birth weight infants in early HAART n/N (%LBW)	*P*	Low birth weight infants with late HAART n/N (%LBW)	*P*
Total	**Total**	173/804 (22)		36/152 (24)		137/652 (21)		69/298 (23)		52/276 (19)	
Demographics	**Maternal age:**										
	16-24	21/123 (17)		5/27 (19)		16/96 (17)		7/46 (15)		8/42 (19)	
	25-29	42/235 (18)		6/31 (19)		36/204 (18)		18/93 (19)		13/85 (15)	
	30-34	61/270 (23)		12/41 (29)		49/229 (21)		27/104 (26)		19/99 (19)	
	≥35	39/130 (30)	0.029	4/11 (36)	0.51	35/119 (29)	0.056	16/51 (31)	0.19	12/50 (24)	0.66
	Race group:										
	Black	62/299 (21)				55/280 (20)		34/158 (22)		14/74 (19)	
	Mixed ancestry	5/8 (63)		7/19 (37)		4/6 (67)		4/5 (80)		0/1 (0)	
	Indian/White	0/3 (0)	0.012	1/2 (50)	0.72	0/3 (0)	0.012	0/0 (0)	0.002	0/2 (0)	0.71
Substance Abuse	**Smoked in pregnancy**:	4/23 (17)	0.79	1/4 (25)	0.92	3/19 (16)	0.73	3/13 (23)	0.77	0/6 (0)	0.25
	Alcohol use in pregnancy:	4/24 (17)	0.72	1/5 (20)	0.85	3/19 (16)	0.74	1/11 (18)	0.90	1/6 (17)	0.93
HIV disease	**WHO stage**:										
	Stage 1 or 2	40/280 (14)		0/2 (0)		40/278 (14)		15/105 (14)		18/147 (12)	
	Stage 3 or 4	25/95 (26)	0.007	0/0 (0)		25/95 (26)	0.008	13/47 (28)	0.049	10/34 (29)	0.013
	CD4 cell count: cells/mm^3										
	0-50	21/62 (34)		2/5 (40)		19/57 (33)		12/31 (39)		3/17 (18)	
	50-100	38/112 (34)		5/16 (31)		33/96 (34)		21/52 (40)		10/37 (27)	
	100-150	37/177 (21)		5/19 (26)		32/158 (20)		16/68 (24)		12/73 (16)	
	150-200	40/237 (17)		8/41 (20)		32/196 (16)		15/85 (18)		15/92 (16)	
	200-250	37/216 (17)	<0.001	16/71 (23)	0.78	21/145 (14)	<0.001	5/62 (8)	<0.001	12/57 (21)	0.65
Health Status	**Hypertension**	17/52 (33)	0.029	1/9 (11)	0.36	16/43 (37)	0.004	10/19 (53)	0.001	4/19 (21)	0.75
	Diabetes history	0/3 (0)	0.37	0/1 (0)	0.58	0/2 (0)	0.47	0/1 (0)	0.59	0/1 (0)	0.63
	Haemoglobin										
	7-11gm/dl	39/209 (19)		6/36 (17)		33/173 (19)		11/62 (23)		14/82 (17)	
	<7gm/dl	4/8 (50)	0.083	0/1 (0)	0.73	4/7 (57)	0.051	3/3 (100)	0.004	1/3 (33)	0.51
	Syphilis serology: positive RPR*	7/18 (39)	0.068	1/3 (33)	0.63	6/15 (40)	0.074	3/6 (50)	0.16	2/7 (29)	0.47
Reproductive Health	**Previous miscarriage**	17/75 (23)	0.65	3/14 (21)	0.79	14/61 (23)	0.52	9/37 (24)	0.86	3/20 (15)	0.88
	Previous preterm birth	7/29 (24)	0.59	0/8 (0)	0.097	7/21 (33)	0.089	2/7 (29)	0.63	4/13 (31)	0.16

*RPR – rapid plasma reagin

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3.4 ASSOCIATION OF STUDY VARIABLES WITH LOW BIRTH WEIGHT AMONG HIV NEGATIVE INFANTS (TABLE 3.4.1)

3.4.1 HIV status of Infants

Among infants with known HIV status, HIV positive infants had higher rates of LBW than HIV negative infants (33% [24/73] vs. 22% [173/804], *P*=0.038).

Among HAART-unexposed infants, those with positive HIV status were associated with LBW (41% [16/39] vs. 24% [36/152], *P*=0.050). Among HAART-exposed infants, slightly more positive infants were LBW but this was not significant (24% [8/34] vs. 21% [137/652], *P*=0.73). No association between positive HIV status and LBW was found in early HAART-exposed (*P*= 0.208) nor late HAART-exposed (*P*=0.74) groups.

When all infants of unknown HIV status were compared to those with negative HIV status, similar rates of LBW were detected (24% [9/37] vs. 24% [36/152], *P*=0.935).

The remainder of the results in this section refers to infants with known HIV negative status. Infants with positive and unknown HIV status were removed before analysis due to the association of HIV and LBW [48].

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3.4.2 Maternal demographic variables

(Table 3.4.1)

Maternal age

On comparison of the ages of women with negative infants, the highest rates of LBW occurred in women of 35 years or older (30% [39/130], *P*=0.029). When ages in individual groups were compared, this finding was most significant in the HAART-exposed infants, where 29% (35/119) of women 35 years or older had LBW infants compared to 19% (101/529) of younger women (*P*=0.02).

Race group

Although most women in the study were black, the small number of women with mixed ancestry had the highest proportion of LBW infants (63% [5/8], *P*=0.012). No Indian or white infants had LBW and 21% (62/299) of black infants were LBW.

3.4.3 Substance use

Smoking

Smoking was not associated with LBW with smokers and non-smokers having similar proportions of LBW negative infants (17% [4/23] vs. 20% [93/474], *P*=0.79).

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Alcohol

Alcohol use was not associated with LBW and the proportion of LBW infants was similar whether women used alcohol or not (17% [4/24] vs. 20% [94/478], *P*=0.72).

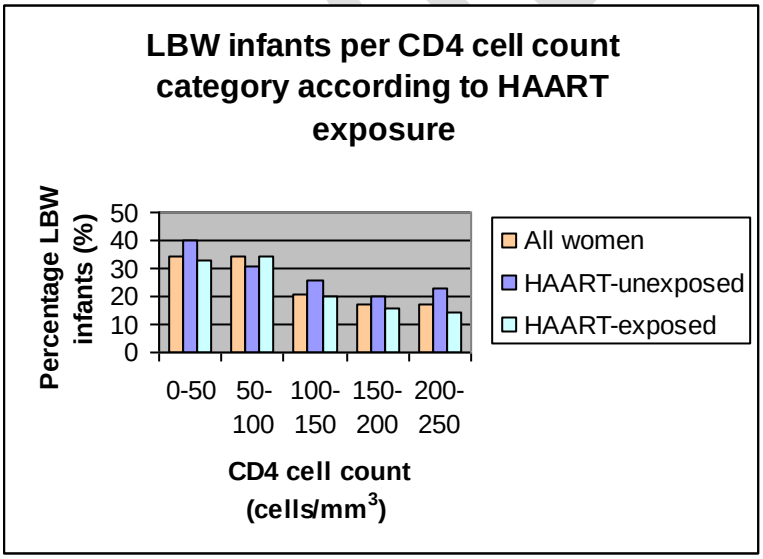
3.4.4 HIV Disease

CD4 cell count

Among women with negative infants, CD4 cell counts below 100cells/mm^3 were associated with LBW (34% [59/174] vs. 18% [114/630], *P*<0.001).

Among HAART-unexposed women, no CD4 cell count range was associated with LBW (*P*=0.78) but a trend of increasing rates of LBW with CD4 decline was evident.

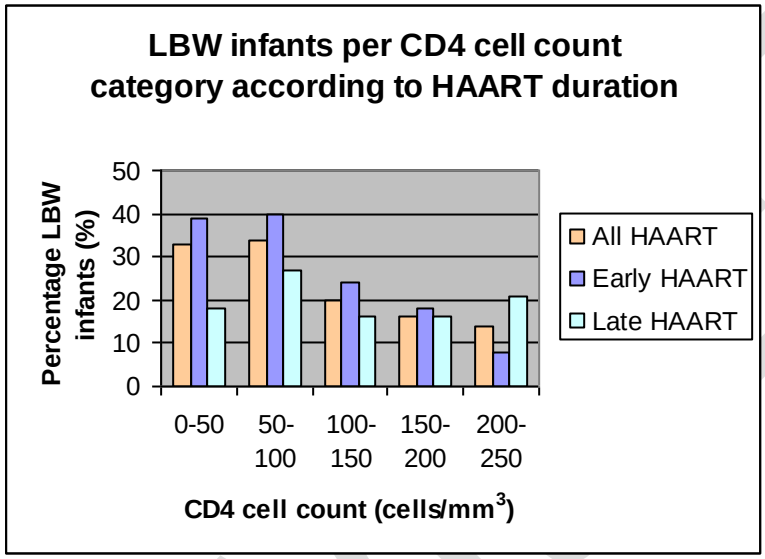
Figure 3.4.1 LBW infants per CD4 cell count category according to HAART exposure



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Among HAART-exposed women, those with CD4 cell counts less than 100cells/mm^3 had more LBW infants than those with higher CD4 cell counts (34% [52/153] vs. 17% [85/499], *P*<0.001). This trend was still significant among women exposed to early HAART (40% [33/83] vs. 17% [36/215], *P*<0.001) but not late HAART (24% [13/54] vs. 18% [39/222], *P*=1.20).

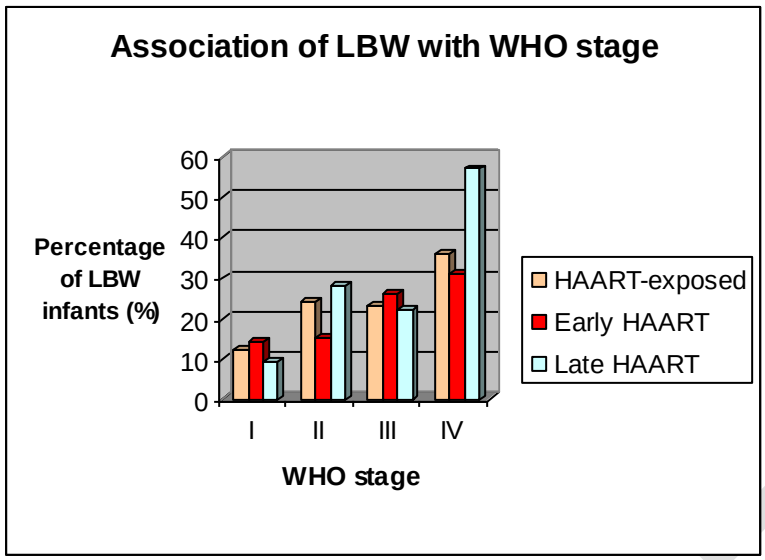
Figure 3.4.2 LBW infants per CD4 cell count category according to HAART duration



WHO clinical stage

Among HAART-exposed women those with more advanced HIV were most at risk for LBW negative infants, with WHO clinical stage 4 women having higher rates of LBW than WHO clinical stages 3 and 2 and WHO clinical stage 1 women having the lowest rate of LBW (36% [8/22] vs. 23% [17/73] vs. 24% [12/50] vs. 12% [28/230], *P*=0.004).

Figure 3.4.3 Association of LBW with WHO stage



Although a similar distribution was found among early HAART-exposed women (see figure 3.4.3), the *P* value was not significant when each of the 4 WHO clinical stages were compared (*P*=0.90). When the WHO clinical stage 1 and 2 women were compared with WHO clinical stage 3 and 4 women , the latter group were more likely to have LBW infants (14% [15/105] vs. 28% [13/47], *P*= 0.049).

Among Late HAART-exposed infants, an association of LBW with advanced WHO clinical stage was also detected (57% stage4 [4/7] vs. 22% stage3 [6/27] vs. 28% stage2 [7/25] vs. 9% stage1 [11/122], *P*=0.001).

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3.4.5 Health Status

Hypertension

When all study women with negative infants were combined, hypertension was associated with LBW (33% [17/52] vs. 20% [102/516], *P*=0.029). An association between hypertension and LBW was found in HAART-exposed (37% [16/43] vs. 19% [82/435], *P*=0.004) and early HAART-exposed women (53% [10/19] vs. 20% [42/210], *P*=0.001). The association between hypertension and LBW was not evident in the HAART-unexposed and late-HAART exposed groups which had small numbers of hypertensive women (*P*=0.36 and 0.75 respectively).

Diabetes History

Incidence of diabetes was very low across all study groups and diabetic history was not associated with LBW among all women (0% [0/3] vs. 21% [120/569], *P*=0.37) nor in any of the study groups.

Haemoglobin

Among all women, anaemia was not associated with LBW (20% [43/217] vs. 22% [55/246], *P*=0.50). When women were divided according to haemoglobin values below and above 7gm/dl, women in the former group tended to have higher rates of LBW and the *P* value approached significance (50% [4/8] vs. 21% [94/455], *P*=0.07).

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No relationship between anaemia and LBW was found in HAART-unexposed women. Only one woman in this group had severe anaemia (*P*=0.73). Among HAART-exposed women, those with severe anaemia had the highest proportion of LBW infants (57% [4/7] vs. 21% [82/393], *P*=0.04).

Among early HAART-exposed women, severe anaemia was associated with LBW (100% [3/3] vs. 20% [33/163], *P*=0.001.This association was not found among late HAART-exposed women (33% [1/3] vs.20% [35/172], *P*=0.50).

Syphilis serology

Among all women, those with a positive RPR had a higher rate of LBW than those with a negative RPR but this was not significant (39% [7/18] vs. 21% [105/502], *P*=0.068). Among the study groups, no clear association with RPR positive result and LBW could be proven

3.4.6 Reproductive Health

Previous Miscarriage

Women who had experienced a previous miscarriage had a similar rate of LBW to those who had not (23% [17/75] vs. 20% [85/417], *P*=0.65). Previous miscarriage was not associated with LBW in any of the study groups.

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Previous Preterm birth

Among all women, those with previous preterm birth were not associated with LBW when compared with women with no such event (24% [7/29] vs. 20% [78/391], *P*=0.59). No association between previous preterm birth and LBW was found in any of the study groups.

Summary of maternal factors associated with LBW

Among women in this study, maternal factors associated with infant LBW included maternal age above 35 years, mixed ancestry (although the numbers were small), CD4 cell count below 100cells/mm^3, WHO clinical stage 4 HIV disease and hypertension. Trends of increased LBW were detected in women with anaemia and positive syphilis serology but these were not significant. The numbers of women who were diabetic, smoked, used alcohol, had a previous miscarriage or had a previous preterm birth were small and no association with LBW and these variables was detected.

WitsETD

Table 3.4.2 Association of HAART and infant outcome variables with low birth weight (LBW) among HIV-negative infants

Variable Category	Variable	LBW infants in all participants n/N (% LBW)	*P* value	LBW infants in HAART-unexposed n/N (% LBW)	*P* value	LBW infants in HAART-exposed n/N (% LBW)	*P* value	LBW infants in early HAART-exposed n/N (% LBW)	*P* value	LBW infants in late HAART-exposed n/N (% LBW)	*P* value
Total	**Total**	173/804 (22)		36/152 (24)		137/652 (21)		69/298 (23)		52/276 (19)	
HAART	**HAART regimen:**										
	unexposed	36/152 (24)		36/152 (24)							
	all HAART-exposed	137/652 (21)	0.54			137/152 (24)		69/298 (24)		52/276 (19)	
	PI-based HAART	59/322 (18)				59/322 (18)		18/104 (17)		33/197 (17)	
	NVP-based HAART	44/238 (18)				44/238 (18)		21/121 (17)		16/66 (24)	
	EFV-based HAART	34/92 (37)	0.001			34/92 (37)	<0.001	30/73 (41)	<0.001	3/13 (23)	0.37
	Duration of HAART:										
	0-3 weeks	28/117 (24)				28/117 (24)		12/61 (20)			
	4-7 weeks	16/129 (12)				16/129 (12)		14/101 (14)			
	8-14 weeks	28/153 (18)				28/153 (18)		30/82 (37)		20/88 (23)	
	15-29 weeks	16/112 (14)				16/112 (14)				12/94 (13)	
	>30 weeks	32/87 (37)	<0.001			32/87 (37)	<0.001		0.001	15/83 (18)	0.22
Infant Outcomes	**Infant gender**:										
	female	79/390 (20)		16/75 (21)		63/315 (20)		32/151 (21)		28/137 (20)	
	male	80/373 (21)	0.69	20/75 (27)	0.44	60/298 (20)	0.97	31/133 (23)	0.67	21/135 (16)	0.30
	Preterm birth:										
	no	102/601 (17)		18/90 (20)		84/511 (16)		32/218 (15)		47/263 (18)	
	yes	34/66 (52)	<0.001	3/4 (75)	0.01	31/62 (50)	<0.001	23/43 (53)	<0.001	5/13 (38)	0.064
	Growth										
	AGA	42/421 (10)		3/55 (5)		39/366 (11)		25/179 (14)		12/172 (7)	
	SGA	83/174 (48)		18/38 (47)		65/136 (48)		24/42 (57)		40/93 (43)	
	LGA	0/26 (0)	<0.001	0/1 (0)	<0.001	0/25 (0)	<0.001	0/19 (0)	<0.001	0/6 (0)	<0.001

PI -protease inhibitor; NVP –nevirapine; EFV- efavirenz; AGA – appropriate for gestational age; SGA – small for gestational age; LGA – large for gestational age

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3.4.7 HAART exposure

(Table 3.4.2)

A similar rate of LBW was found in HAART-unexposed and HAART-exposed negative infants (24% [36/152] vs. 21% [137/652], *P*=0.54).

Early HAART-exposed infants were not more at risk for LBW than late HAART-exposed infants (24% [69/292] vs. 19% [52/276], *P*=0.20).

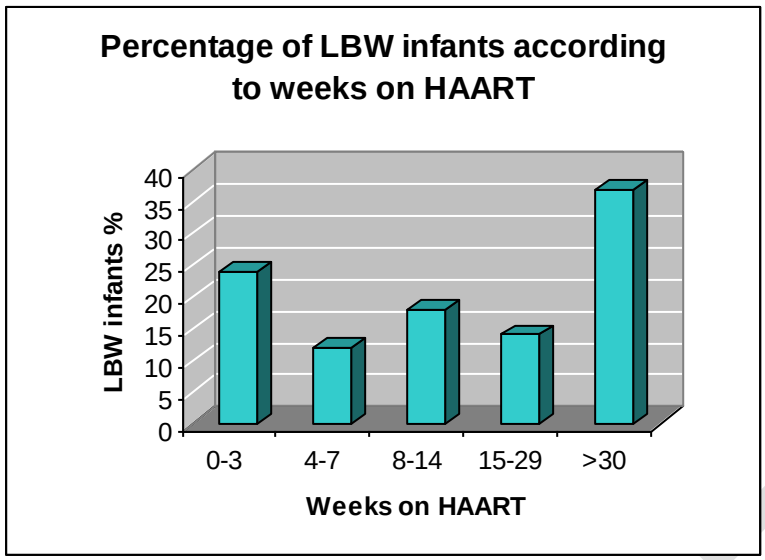
EFV-exposure was associated with LBW compared to PI-exposure and NVP-exposure (37% [34/92] vs. 18% [59/322] vs. 18% [44/238], *P*=0.001). Early EFV-exposure was particularly associated with LBW (41% [30/73] vs. 17% [18/104] vs. 17% [21/121], *P*<0.001) while late EFV-exposure was not (23% [3/13] vs. 17% [33/197] vs. 24% [16/66], *P*=0.37).

Duration of HAART exposure

The risk of LBW according to duration of HAART exposure had a bimodal distribution with the highest rates of LBW found in women who received HAART for longest (>30 weeks) and shortest (0 to 3 weeks) durations (37% [32/87] and 24% [28/117]). The lowest rate of LBW was found in women who received HAART for 4-7 weeks followed by the women who received 15-29 weeks and then 8-14 weeks of HAART (12% [16/129] vs. 14% [16/112] vs.18% [28/153], *P*<0.001). (See graph).

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Figure 3.4.4 Association of LBW with WHO stage



3.4.8 Infant outcomes

Infant gender

Rates of LBW for male versus female negative infants did not differ across all the groups with 20% (79/390) of all female infants and 21% (80/373) of all male infants having LBW (*P*=0.69).

Preterm birth

As expected, negative preterm Infants had a higher rate of LBW than their term counterparts and this was true across all groups.

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Growth

As expected, infants with SGA were most associated with LBW versus those with AGA or LGA and this was true across all groups.

Summary of association of Infant and HAART variables with LBW

HAART-exposed women had similar rates of LBW compared to HAART-unexposed women. When different durations of HAART exposure were compared, women exposed to less than 7 weeks or more than 30 weeks of HAART were most likely to have LBW infants. Among HAART exposed women, those exposed to early EFV-based regimens had the highest rates of LBW.

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3.5 ASSOCIATION OF STUDY VARIABLES WITH PRETERM BIRTH

3.5.1 Maternal demographic variables

(Table 3.5.1)

Maternal age

On comparison of all women, no particular age range was found to be associated with preterm births. In women exposed to early HAART, the highest rates of preterm birth occurred in women of 35 years or older (32% [23/71], *P*=0.031).

Race group

No clear association with race group and preterm birth was detected.

3.5.2 Substance use

Smoking

Smoking was not associated with preterm birth with smokers and non-smokers having similar proportions of preterm infants (10% [3/31] vs. 12% [88/750], *P*=0.73).

Alcohol

Alcohol use was not associated with preterm birth and the proportion of preterm infants was similar whether women used alcohol or not (10% [3/30] vs. 12% [88/760], *P*=0.79).

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3.5.3 HIV Disease

CD4 cell count

Women with CD4 cell counts below 100cells/mm^3 were associated with preterm birth (20% [47/235] vs. 11% [98/858], *P*=0.001).

WHO clinical stage

WHO clinical stage was only available for HAART-exposed women. Women with WHO stage 4 were most at risk for preterm infants (26% [9/35], *P*=0.035).

3.5.4 Health Status

Tuberculosis

TB history was only available for 121 HAART-exposed women. No association between preterm birth and TB was detected (28% [15/54] vs. 21% [52/67], *P*=0.28.

Hypertension

When all study women were combined, hypertension was not associated with preterm birth (17% [14/83] vs. 12% [99/794], *P*=0.26) but an association between hypertension and preterm birth was found in early HAART-exposed women (38% [11/29] vs. 19% [56/290], *P*=0.019).

Diabetes History

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Incidence of diabetes was very low across all study groups and diabetic history was not associated with preterm birth among all women (0% [0/4] vs. 13% [115/876], *P*=0.44) nor in any of the study groups.

Haemoglobin

Anaemia was not associated with preterm birth among any of the study groups.

Syphilis serology

Among the study groups, no clear association with RPR positive result and preterm birth could be proven

3.5.5 Reproductive Health

Previous Miscarriage

Women who had experienced a previous miscarriage had a similar rate of preterm birth to those who had not (13% [16/127] vs. 11% [68/642], *P*=0.51). Previous miscarriage was not associated with preterm birth in any of the study groups.

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Previous Preterm birth

Among all women, those with previous preterm birth were associated with preterm birth when compared with women with no such event (20% [10/50] vs. 9% [56/626], *P*=0.011). This association was also detected in women exposed to HAART (26% [9/34] vs. 10% [50/501], P=0.003) and women exposed to early HAART (42% [5/12] vs. 13% [23/179], P=0.006).

Summary of maternal factors associated with preterm birth

Among women in this study, maternal factors associated with infant preterm birth included low CD4 cell count, advanced WHO clinical stage and previous preterm birth. No association with preterm birth was detected in women who ever had TB, were anaemic, were diabetic, had positive syphilis serology, smoked, used alcohol or had a previous miscarriage.

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Table 3.5.1 Association of demographic and maternal health variables with preterm birth

Variable Category	Variable	Preterm birth infants in all participants n/N (% prem)	*P*	Preterm birth infants in HAART-unexposed n/N (% prem)	*P*	Preterm birth infants in HAART-exposed group n/N (% prem)	*P*	Preterm birth infants in early HAART n/N (% prem)	*P*	Preterm birth infants with late HAART n/N (% prem)	*P*
Total	**Total**	145/1093 (13)		7/147 (5)				81/389 (21)		21/427 (5)	
Demographics	**Maternal age:**										
	16-24	19/182 (10)		1/30 (3)		18/152 (12)		11/53 (21)		1/77 (1)	
	25-29	43/345 (12)		4/45 (9)		39/300 (13)		19/131 (15)		12/128 (9)	
	30-34	52/369 (14)		1/51 (2)		51/318 (16)		28/131 (21)		7/146 (5)	
	≥35	31/192 (16)	0.39	1/20 (5)	0.44	30/172 (17)	0.37	23/71 (32)	0.031	1/75 (1)	0.022
	Race group:										
	Black	86/453 (19)		0/29 (0)		86/424 (20)		50/217 (23)		10/120 (8)	
	Mixed ancestry	2/11 (18)		1/2 (50)		1/9 (11)		1/5 (20)		0/2 (0)	
	Indian/White	0/4 (0)	0.63	0/0 (0)	<0.001	0/4 (0)	0.48	0/0 (0)	0.873	0/3 (0)	0.80
Substance Abuse	**Smoked in pregnancy**:										
	yes	3/31 (10)		1/6 (17)		2/25 (8)		2/15 (13)		0/7 (0)	
	no	88/750 (12)	0.73	5/128 (4)	0.14	83/622 (13)	0.44	46/243 (19)	0.59	13/305 (4)	0.58
	Alcohol use in pregnancy:										
	Yes	3/30 (10)		1/7 (14)		2/23 (9)		1/15 (7)		0/7 (0)	
	no	88/760 (12)	0.79	6/131 (5)	0.25	82/629 (13)		47/246 (19)	0.23	13/308 (4)	0.58
HIV disease	**WHO stage**:										
	Stage 1	34/310 (11)				34/310 (11)		21/111 (19)		6/180 (3)	
	Stage 2	7/64 (11)				7/64 (11)		5/25 (20)		0/35 (0)	
	Stage 3	19/104 (18)		No observations		19/104 (18)		11/43 (26)		2/43 (5)	
	Stage 4	9/35 (26)	0.035			9/35 (26)	0.035	5/15 (33)	0.55	2/12 (17)	0.066
	CD4 cell count: cells/mm^3										
	0-50	15/77 (19)		0/2 (0)		15/75 (20)		13/40 (33)		1/28 (4)	
	50-100	32/158 (20)		2/16 (13)		30/142 (21)		19/63 (30)		4/62 (6)	
	100-150	36/253 (14)		3/20 (15)		33/233 (14)		18/91 (20)		7/108 (6)	
	150-200	32/318 (10)		1/43 (2)		31/275 (11)		14/107 (13)		5/136 (4)	
	200-250	30/287 (10)	0.006	1/66 (2)	0.063	29/221 (13)	0.050	17/88 (19)	0.03	4/93 (4)	0.83

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Table 3.5.1 (continued)

Variable Category	Variable	Preterm birth infants in all participants n/N (% prem)	*P*	Preterm birth infants in HAART-unexposed n/N (% prem)	*P*	Preterm birth infants in HAART-exposed group n/N (% prem)	*P*	Preterm birth infants in early HAART n/N (% prem)	*P*	Preterm birth infants with late HAART n/N (% prem)	*P*
Total	**Total**	145/1093 (13)		7/147 (5)				81/389 (21)		21/427 (5)	
Health Status	**Hypertension**										
	yes	14/83 (17)		0/16 (0)		14/67 (21)		11/29 (38)		2/27	
	no	99/794 (12)	0.26	6/122 (5)	0.36	93/672 (14)	0.12	56/290 (19)	0.019	15/314	0.54
	Diabetes history										
	yes	0/4 (0)		0/1 (0)		0/3 (0)		0/1 (0)		0/2 (0)	
	no	115/876 (13)	0.44	7/139 (5)	0.82	108/740 (15)	0.118	67/318 (21)	0.61	17/432 (5)	0.75
	Haemoglobin										
	>11gm/dl	51/361 (14)		2/43 (5)		49/318 (15)		1/4 (25)		5/146 (3)	
	7-11gm/dl	40/319 (13)		1/53 (2)		39/266 (15)		20/90 (22)		7/134 (5)	
	<7gm/dl	2/13 (15)	0.81	0/2 (0)	0.71	2/11 (18)	0.93	31/133 (23)	0.98	1/6 (17)	0.27
	Syphilis serology:										
	positive RPR*	7/34 (21)		0/3 (0)		7/31 (23)		3/10 (30)		0/11 (0)	
	negative RPR	90/765 (12)	0.12	7/129 (5)	0.68	83/636 (13)	0.13	44/216 (20)	0.46	15/328 (5)	0.47
Reproductive Health	**Gravidity**										
	gravida 1	9/127 (7)		1/21 (5)		8/106 (8)		7/42 (17)		1/57 (2)	
	gravida 2	47/339 (14)		3/52 (6)		44/287 (15)		25/116 (22)		9/140 (6)	
	gravida 3	37/273 (14)		3/42 (7)		34/231 (15)		18/101 (18)		5/98 (5)	
	gravida≥4	21/163 (13)	0.24	0/27 (0)	0.59	21/136 (15)	0.22	17/66 (26)	0.57	2/59 (3)	0.52
	Previous miscarriage										
	yes	16/127 (13)		3/27 (11)		13/100 (13)		10/52 (19)		2/38 (5)	
	no	68/642 (11)	0.51	4/112 (4)	0.11	64/530 (12)	0.80	31/197 (16)	0.55	13/272 (5)	0.90
	Previous preterm birth										
	yes	10/50 (20)		1/16 (6)		9/34 (26)		5/12 (42)		2/18 (11)	
	no	56/626 (9)	0.011	6/125 (5)	0.80	50/501 (10)	0.003	23/179 (13)	0.006	10/263 (4)	0.14

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3.5.6 HAART exposure

(Table 3.5.2)

A higher rate of preterm birth was found in HAART-exposed compared to HAART-unexposed infants (15% [138/946] vs. 5% [7/147], *P*<0.001).

Early HAART-exposed infants were more at risk for preterm birth than late HAART-exposed infants (21% [81/389] vs. 5% [21/427], *P*<0.001).

PI-exposure was less associated with preterm birth than NVP and EFV-exposure (9% [44/474] vs. 19% [63/336] vs. 23% [31/136], *P*<0.001).

Duration of HAART exposure

Women who had received HAART for more than 30 weeks were at highest risk for preterm birth (22% [20/92], *P*=0.002). (see table 4.2)

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Table 3.5.2 Association of HAART and infant outcome variables with preterm birth

Variable Category	Variable	Preterm infants in all participants n/N (% prem)	*P* value	Preterm infants in HAART-unexposed n/N (% prem)	*P* value	Preterm infants in HAART-exposed n/N (% prem)	*P* value	Preterm infants in early HAART-exposed n/N (% prem)	*P* value	Preterm infants in late HAART-exposed n/N (% prem)	*P* value
Total	**Total**	145/1093 (13)		7/147 (5)		138/946 (15)		81/389 (21)		21/427 (5)	
HAART	**HAART regimen:**										
	unexposed	7/147 (5)		7/147 (5)							
	all HAART-exposed	138/946 (15)				138/946 (15)		81/389 (21)		21/427 (5)	
	PI-based HAART	44/474 (9)				44/474 (9)		19/131 (15)		9/290 (3)	
	NVP-based HAART	63/336 (19)				63/336 (19)		40/167 (24)		11/116 (9)	
	EFV-based HAART	31/136 (23)	<0.001			31/136 (23)	<0.001	22/91 (24)	0.091	1/21 (5)	0.027
	Duration of HAART:										
	0-3 weeks	21/169 (12)				21/169 (12)		8/21 (38)		10/142 (7)	
	4-7 weeks	9/172 (5)				9/172 (5)		2/16 (13)		7/148 (5)	
	8-14 weeks	25/214 (12)				25/214 (12)		22/88 (25)		3/12 (2)	
	15-29 weeks	15/141 (10)				15/141 (10)		15/134 (11)		0/4 (0)	
	>30 weeks	20/92 (22)	0.002			20/92 (22)	0.002	20/91 (22)	0.010		0.36
Infant Outcomes	**Infant gender**:										
	female	60/501 (12)		3/71 (4)		57/430 (13)		38/185 (20)		10/205 (5)	
	male	60/500 (12)	0.99	4/74 (5)	0.74	56/426 (13)	0.96	31/173 (18)	0.53	9/204 (4)	0.82
	Low Birth Weight:										
	no	57/794 (7)		2/104 (2)		55/635 (8)		25/267 (9)		12/331 (4)	
	yes	61/217 (28)	<0.001	4/40 (10)	0.03	57/177 (32)	<0.001	35/74 (47)	<0.001	7/76 (9)	0.037

PI -protease inhibitor; NVP –nevirapine; EFV- efavirenz;

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3.5.7 Infant outcomes

Infant gender

Rates of preterm birth for male versus female negative infants did not differ across all the groups with 12% (60/501) of all female infants and 12% (60/500) of all male infants having preterm birth (*P*=0.99).

Low birth weight

As expected, low birth weight infants had a higher rate of preterm births than their heavier counterparts and this was true across all groups.

Summary of association of Infant and HAART variables with preterm birth

HAART-exposed women had higher rates of preterm birth compared to HAART-unexposed women. When different durations of HAART exposure were compared, women exposed to more than 30 weeks of HAART were most likely to have preterm infants. Among HAART exposed women, those exposed to NNRTI-based regimens had the highest rates of preterm birth.

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3.6 MULTIVARIATE ANALYSIS OF LBW

(Table 3.6)

Table 3.6 Multivariate logistic regression showing risk factors for LBW in HAART-exposed women.

Variable	Low Birth Weight (<2500g)											
	Early HAART						Late HAART					
	Univariate analysis			Multivariate analysis			Univariate Analysis			Multivariate Analysis		
	OR	CI (95%)	*P* value	AOR	CI	*P* value	OR	CI (95%)	*P* value	AOR	CI	*P* value
HAART-unexposed	1.00			1.00			1.00			1.00		
HAART-exposed												
PI-based HAART	0.67	0.36-1.27	0.22	0.44	0.19-1.05	0.064	0.65	0.38-1.10	0.11	0.52	0.26-1.05	0.068
NVP-based HAART	0.68	0.37-1.23	0.20	0.37	0.17-0.83	0.015	1.03	0.52-2.03	0.93	1.02	0.46-2.31	0.94
EFV-based HAART	2.25	1.24-4.09	0.008	1.00	0.45-2.23	1.0	0.97	0.25-3.70	0.96	0.55	0.10-2.97	0.49
CD4 cell count per category increase*	0.70	0.59-0.83	<0.001	0.58	0.46-0.73	<0.001	0.94	0.77-1.15	0.54	0.92	0.71-1.18	0.50
Maternal age per year increase	1.06	1.01-1.11	0.015	1.06	1.00-1.12	0.043	1.04	0.99-1.09	0.14	1.04	0.98-1.10	0.16
Hypertension	2.39	1.06-5.37	0.035	2.38	0.99-5.73	0.054	0.87	0.31-2.38	0.78	0.72	0.25-2.05	0.53

HAART, antiretroviral therapy; PI, Protease inhibitor; NVP, Nevirapine; EFV, Efavirenz; OR, odds ratio; AOR adjusted odds ratio; CI (95%), 95% confidence interval * CD4+ categories (cells/mm3): 0-49, 50-99, 100-149, 150-199 and 200-250

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3.6.1 Early HAART

In unadjusted analysis of women exposed to early HAART, EFV-based HAART and hypertension were the only variables associated with LBW. After adjusting for regimen type, CD4 category, maternal age and hypertension, only hypertension was associated with LBW and the association of EFV-based HAART and LBW was no longer detected. A rise in CD4 category was protective against LBW. Nevirapine-based HAART was associated with a reduction in LBW (OR 0.37, 95% CI 0.17-0.83, P=0.02), a similar odds as PI-containing regimens (0.44, 95%CI=0.19-1.05).

3.6.2 Late HAART

No clear associations between the risk factors analysed and LBW were found in the group of women exposed to late HAART. Women exposed to PI-based HAART had the lowest AOR (adjusted odds ratio) for LBW and the *P* value approached significance (*P*=0.068).

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3.7 MULTIVARIATE ANALYSIS OF PRETERM BIRTH

Table 3.7 Multivariate logistic regression showing risk factors for preterm birth in HAART-exposed women.

Variable	Preterm Birth (<37weeks)											
	Early HAART						Late HAART					
	Univariate analysis			Multivariate analysis			Univariate Analysis			Multivariate Analysis		
	OR	CI (95%)	*P*	AOR	CI	*P*	OR	CI (95%)	*P*	AOR	CI	*P*
HAART-												
Unexposed	1.00			1.00			1.00			1.00		
Exposed:												
PI-based	3.39	1.38-8.36	0.008	3.00	1.07-8.38	0.036	0.64	0.23-1.76	0.39	0.70	0.23-2.13	0.53
NVP-based	6.30	2.72-13.56	<0.001	5.41	2.14-13.70	<0.001	2.10	0.79-5.59	0.14	1.88	0.61-5.80	0.27
EFV-based	6.40	2.60-15.65	<0.001	5.64	2.09-15.16	0.001	1.00	0.12-8.56	1.00	1.47	0.15-14.10	0.74
CD4 cell count												
0-49cells/mm^3	1.00			1.00			1.00			1.00		
per category increase*	0.69	0.58-0.83	<0.001	0.68	0.55-0.85	0.001	0.78	0.57-1.07	0.12	0.80	0.55-1.15	0.22
Maternal age												
16-24 years	1.00			1.00			1.00			1.00		0.03
25-29 years	0.90	0.42-1.89	0.76	0.91	0.37-2.21	0.83	5.35	1.2-23.75	0.027	9.17	1.17-72.0	5
30-34 years	1.12	0.54-2.33	0.76	1.08	0.45-2.57	0.86	2.22	0.46-10.66	0.32	3.46	0.41-29.45	0.26
≥35 years	2.12	0.98-4.57	0.056	2.09	0.83-5.25	0.12	1.13	0.16-8.18	0.90	1.91	0.17-21.66	0.60
Hypertension												
no	1.00			1.00			1.00			1.00		
yes	1.83	0.88-3.80	0.11	1.95	0.87-4.36	0.11	0.96	0.22-4.26	0.96	0.84	0.18-3.90	0.83

3.7.1 Early HAART

In univariate analysis evaluating associations between HAART and preterm birth in all infants (regardless of HIV status), significant associations were detected in the early HAART group between HAART-exposure (to any HAART-regimen) and maternal CD4 count. Of the regimens, NNRTI-based regimens were most associated with preterm birth and this association remained in multivariate analysis. In the early HAART group, every 50 cell rise in CD4+ cell count was associated with a 31% decrease in the odds of preterm birth in univariate analysis (95% CI 0.58-0.83, P<0.001) and remained significant after multivariate

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analysis (AOR 0.68, 95% CI 0.55-0.85, P=0.001) . Neither smoking nor alcohol was associated with preterm birth in this analysis.

3.7.2 Late HAART

No clear associations between the risk factors analyzed and LBW were found in the group of women exposed to late HAART.

3.8 SUMMARY OF RESULTS

Among this cohort of women with advanced HIV disease, HAART-exposed women were found to be older and have lower immunity than HAART-unexposed women. HAART exposed women had increased preterm birth rates and decreased LBW rates compared to HAART-unexposed women. HAART-unexposed women had higher rates of SGA infants. PI-exposed women did not have increased preterm birth rates compared to other regimens.

Women exposed to EFV-based HAART had the most clinically and immunologically advanced HIV disease, the highest rate of TB history and the longest median duration of HAART exposure of any regimen. After adjusting for CD4 category, maternal age and hypertension EFV-based HAART was not found to be associated with LBW.

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CHAPTER 4

4.0 DISCUSSION

4.1 INTRODUCTION

This study set out to explore birth outcomes associated with *in-utero* HAART exposure in the context of non-research clinical settings in Johannesburg South Africa where women were only initiated on HAART if they had advanced immuno-suppression. The hope was to help inform HIV clinicians working with pregnant women in similar settings about the safety of the regimens available as well as the relationship between duration of regimen and adverse outcomes.

4.2 INFANT OUTCOMES

4.2.1 Gestation

In this cohort of HIV-infected, immunocompromised women, HAART-exposure was associated with an increased risk of preterm birth. This supports previous studies by Lorenzi [5], Thorne [7], Cotter [9] and Townsend [17] which demonstrated an association between *in-utero*-HAART exposure and preterm birth. An important difference in our study is that it examined this association in women with low immunity thus on the one hand controlling for the influence of CD4 cell count on risk for preterm birth but on the other hand making the findings applicable to that group only. Additionally, rates of smoking and alcohol use across

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all our groups were low, unlike many European and North American studies, where rates of smoking have ranged from 7.5% to 55% [14,19,34]. A longer exposure to HAART was linked with increased risk of preterm birth but since women who initiated HAART after 28 weeks had already achieved the third trimester of their pregnancy, this finding should be viewed with this in mind.

Contrary to other studies by Lorenzi [5] and Cotter[9], we did not find PI-based HAART to be particularly associated with preterm birth compared to other regimens. What may explain this finding is that unlike previous studies, PI-exposure was not associated with advanced HIV disease, itself a risk factor for preterm birth. Another important difference is that our study only used boosted PIs (lopinavir/ritonavir combination) compared to previous studies which used mainly unboosted PIs [5, 9]. It is possible that boosted PIs are less likely to influence birth outcomes because they allow for lower dosage without compromising drug efficacy and therefore have decreased adverse effects.

In our study NNRTI-exposed women experienced more preterm births than PI-exposed women. The women exposed to NNRTIs were more likely to have attended JH and therefore had more complicated pregnancies including increased rates of hypertension and previous miscarriage. In Addition, efavirenz-exposed women had more advanced HIV than women on other regimens, and early efavirenz- exposed women had been on HAART longer than other groups (62.7 weeks vs. 16 weeks), both factors put these women at risk for preterm births. In multivariate analysis with these co-variates included, there was a small attenuation in the odds ratio (from 6.4 to 5.6); however, the association of early efavirenz with preterm delivery

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remained strongly significant (*P*=0.001). This explains the dissipation of effects in adjusted models.

Unlike Thorne [7] and Townsend's [17] findings, the rate of extreme preterm birth was not significantly increased with HAART-exposure. However early HAART-exposure was associated with higher extreme premature birth rate when compared to late HAART-exposure. These findings suggest that HAART may pose some risk for extremely premature birth but our study was not adequately powered to detect this.

Rates of smoking and alcohol use across all groups were found to be low. No women were identified as users of illicit substances. The latter may be expected in a community where HIV is predominantly spread through heterosexual contact. Unlike many European and North American studies [8, 14, 17, 19, 34] the birth outcomes in our study are not confounded by illicit substance use during pregnancy, which is a cause of preterm birth [28].

Many of the studies which found an association between preterm birth and HAART exposure did not take into account previous preterm birth as a risk factor [7, 13]. An exception to this was the study by Cotter [9]. Our study found a higher rate of previous preterm birth in the HAART-unexposed women while HAART-exposed women experienced more preterm births in their index pregnancy. This suggests HAART as an independent risk factor for preterm birth.

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4.2.2 Birth weight

The finding of a lower mean birth weight and a higher rate of LBW in HAART-unexposed infants seems contradictory to the association of HAART-exposure and preterm birth. However, it was found that HAART-unexposed women had higher rates of SGA infants. The rate of LBW of all study infants (22%) was higher than the rate of 15% predicted by UNICEF [29] for South Africa but for different reasons. HAART-exposed infants were more likely to be born preterm while HAART-unexposed infants were more likely to be SGA. While HAART caused a mild degree of preterm birth, it was protective against HIV transmission and intrauterine growth restriction in infants born to women with low immunity. This highlights the importance of HIV positive women with low CD4 cell counts accessing HAART early in pregnancy for the sake of their own and their infant's health.

Many of the factors associated with LBW in this study, such as maternal age, CD4 cell count and hypertension, have been reported in previous studies [48]. Despite findings from a variety of other settings, in our cohort lopinavir/ritonavir exposure was not associated with LBW in early or late HAART-exposed women. We did detect some association of LBW with efavirenz, which did not persist after controlling for stage of HIV infection and TB, factors linked to poor obstetric outcomes, including LBW [53,54]. Unexpectedly, in the early HAART group, nevirapine was found to decrease the odds of LBW. Nevirapine has previously been associated with increased risk of LBW [54] as well as found to be neutral with respect to LBW [70]. To our knowledge this data is the first to describe a protective effect. This could be due to the fact that untreated advanced HIV infection (CD4 count <250 cells/mm^3) confers increased risk for low birth weight, and initiation of treatment lowers this risk. There could

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also be site specific reasons why NNRTIs and not PIs were significant in this analysis. Women started on NNRTIs tended to be from JH, which handled more complicated pregnancies. Therefore, the protective effect of NNRTI on birth weight may be seen in the setting of the high risk of LBW in women at JH with both advanced HIV and complicated pregnancies. In contrast with previous studies, we did not find associations with LBW and previous preterm birth, previous miscarriage, anaemia, and syphilis [28,58].

Only 26 study infants were VLBW. Women with VLBW infants were more likely to be from RM, a site that has an integrated approach to the care of HIV-infected infants in the neonatal intensive care unit (ICU). CMJH does not have a specific linkage between HIV and neonatal ICU care, increasing the likelihood that these infants could have been lost to follow-up and not included in the database. In the small group of VLBW infants identified, no association was detected with maternal immunological status [48]. Neither HAART duration (early vs. late) nor regimen emerged as a risk factor for VLBW. Small numbers of VLBW infants limit this analysis.

4.2.3 Head circumference

In addition to having a higher mean birth weight, HAART-exposed infants had a higher mean head circumference than HAART-unexposed infants. This suggests that the HAART – unexposed infants had a degree of intrauterine growth restriction which affected skull growth as well as weight. This resulted in a pattern of symmetrical growth restriction and implies that these infants experienced slowing in growth from early on in pregnancy. Therefore our

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findings suggest that maternal HAART could protect against symmetrical growth restriction in foetuses of immunologically suppressed women.

4.2.4 Infant HIV status

Infants whose mothers missed the opportunity for HAART had a much higher rate of positive HIV test than those who accessed HAART (19% vs. 5%, *P*<0.001). The use of single dose NVP among the HAART-unexposed women was not known but probably accounted for their transmission rate being slightly lower than some studies of infants with no antiretroviral exposure. One such study, the first study to show a reduction in MTCT using AZT, showed an HIV transmission rate of 25.5% in its placebo arm [55]. Early HAART was associated with a lower rate of HIV positive infants than late HAART (2% vs. 9%, *P*<0.001). This is congruent with the finding that the longer the exposure to HAART, the more time allowed for viral suppression and the lower the HIV transmission [56, 57]. No regimen was found to be superior in terms of HIV transmission for early or late HAART exposure.

4.3 DESCRIPTION OF STUDY POPULATION

4.3.1 HAART exposed versus HAART-unexposed

In this study women exposed to HAART had a mean age 1.4 years older, a lower median CD4 count and higher median haemoglobin level than HAART-unexposed women. Possibly, older women were more likely to attend antenatal clinic and access HAART than younger women. Women with lower CD4 cell counts may have had more clinical stigmata of HIV and been more inclined to seek health care for themselves. HAART may have had a protective

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effect on the development of anaemia during pregnancy but must be seen in the context of this study. Many of the HAART-unexposed women had not attended antenatal clinic and not received iron and folate supplementation which would also predispose them to lower haemoglobin levels. Previously, extremes of maternal age, low CD4 counts and low haemoglobin levels have been linked with preterm birth and LBW [28] After controlling for age and CD4 count in the multivariate analysis, we did not find HAART-exposure to be associated with LBW.

Many HAART-unexposed women had not accessed antenatal care and probably had poor health seeking behaviour which could have adversely affected the outcomes of their previous and current pregnancies. This may have contributed to the slightly higher previous preterm pregnancy rate in the HAART-unexposed versus HAART-exposed women (*P*=0.055). Despite having more risk factors such as a higher rate of anaemia and previous preterm pregnancy, the HAART-unexposed women had a lower rate of preterm birth than the HAART-exposed women. This suggests HAART as an independent risk factor for preterm birth.

Women exposed to early HAART had a higher previous miscarriage rate than those exposed to late HAART. Previous miscarriage has been identified as a risk factor for preterm delivery and could therefore have been a confounder when rates of preterm birth in these groups were compared [28, 58].

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In summary, HAART-exposed women were slightly older, had immunologically more advanced HIV, fewer previous preterm deliveries and higher haemoglobin values than HAART-unexposed women. More women exposed to early HAART were black, and had more previous miscarriages than those exposed to late HAART.

4.3.2 Rahima Moosa Hospital versus Charlotte Maxeke Johannesburg Academic Hospital

RM had a greater proportion of women exposed to PI-based HAART than JH due to the prescribing protocol at that hospital. The highest rate of PI-used was found in women exposed to late HAART since those exposed to early HAART may already have been taking NNRTI-based regimens when they found out they were pregnant.

JH had a greater proportion of women exposed to NNRTI-based HAART, most women in the late HAART-exposed group using NVP (92% of late HAART) and most women in the early HAART-exposed group using EFV (79% of early HAART). This could be because many women in the early HAART group were already on EFV when they fell pregnant and only presented to clinic subsequent to the first trimester and therefore left on EFV, while the late HAART group were mainly initiated on NVP as per that clinic's protocol.

Almost all (99%) of the women from JH were black due to the areas which refer to this hospital housing predominantly black communities. In contrast, RM had a few more women

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of mixed ancestry and Indian or white women due to the nature of the surrounding communities of the hospital.

RM hospital had a greater amount of women in WHO clinical stage 1 (73%) than JH hospital (46%, $P<0.001$). This could be due to JH antenatal clinic being a referral centre for more complicated patients as well as pregnant patients from the JH adult antiretroviral clinic. Patients attending an ARV clinic tend to have more clinically advanced HIV than women who have been identified as HIV positive through antenatal screening. Since most of the RM women were on PI-based HAART, this regimen was associated with less advanced HIV than other regimens.

A higher rate of alcohol use was detected in HAART-exposed women at JH than RM hospital ($P=0.001$). This result should be viewed in the context of limited data and low rates of alcohol use at both hospitals

Among HAART-exposed women, more PI-exposed women (79%) had vaginal births than NVP (65%) and EFV-exposed (64%) women ($P<0.001$). This is consistent with JH hospital having more complicated pregnancies and deliveries than RM.

The differences in prescribing protocols at the two hospitals could have affected the study outcomes. Women from JH tended to have more complicated pregnancies. They were more likely to be black, use alcohol (although rate of alcohol use in the whole cohort was extremely

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low), have previous hypertension or diabetes, have increased gravidity and have had a previous miscarriage. JH women also had a more advanced clinical stage of HIV than RM women. NVP and EFV were more likely to be prescribed at JH, so many of the same variables were more common in women on these regimens. The patient population of JH may have been prone to preterm deliveries for reasons other than their HAART regimen.

4.3.3 Efavirenz exposure

In this cohort, EFV-exposed women emerged as a distinct group with more risk factors for poor obstetric outcomes therefore higher rates of preterm birth and low birth weight infants than other regimens. A high percentage of EFV-based HAART exposed women were in WHO clinical stage 3 (61% of late HAART-exposed and 33% of early HAART-exposed) which was congruent with the preferred use of EFV in the presence of TB co-infection (WHO clinical stage 3 condition). The use of EFV in women with co-morbidity such as TB or liver disease, could also account for the lower median CD4 cell count and higher previous preterm birth rate detected in this group. However, when CD4 cell count, age and hypertension were controlled for, EFV use was no longer associated with LBW.

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Among women exposed to late HAART, the duration of HAART exposure in weeks was similar for all regimens. Among women exposed to early HAART, the median weeks of exposure were much longer for EFV (62.7) than for PIs (17.1) or NVP (15.6). This indicates that a large number of women fell pregnant while on EFV but were only detected as pregnant after the first trimester. Although reassuring that none of the EFV-exposed infants in this

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study had neural tube defects, EFV has been implicated as a potential teratogen in monkey studies [59-61] . Thus far in humans, four retrospective case of central nervous system defects in infants with first trimester exposure to EFV have been reported (three with meningomyelocele and one with a Dandy-Walker malformation) causing EFV to be changed from Pregnancy Category C to D [59, 62, 63] .The current antiretroviral prescribing guidelines allow for EFV to be prescribed to fertile women with adequate counselling about contraception [40]. In light of the many failures of contraception detected in this study, further study is necessary and these guidelines may need to be revised.

4.4 ASSOCIATION OF VARIABLES WITH LOW BIRTH WEIGHT

4.4.1 Variables associated with LBW

The association of study variables was investigated among negative infants because positive infants are more likely to have LBW [48]. Once the infants with positive or unknown HIV status were removed, the following variables were found to be associated with LBW:

- Maternal age 35 years or older
- Maternal CD4 cell count below 100cells/mm^3
- Preterm infants
- SGA infants
- Early EFV exposure
- Maternal HAART exposure >30 weeks or < 3 weeks
- Maternal mixed ancestry
- Advanced WHO clinical stage

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- Maternal hypertension

Many of these findings were in agreement with previous studies which have identified high maternal age, preterm birth, intrauterine growth restriction and maternal hypertension as risk factors for LBW [28]. After controlling for regimen type, CD4 cell count and maternal age, hypertension remained the variable most associated with LBW in the group of women exposed to early HAART.

Contrary to previous studies, PI-exposure was not associated with LBW in early or late HAART-exposed women and seemed to be protective against LBW in the late group even after controlling for maternal CD4 cell count, age and hypertension. Additionally, in the early HAART group, nevirapine was found to decrease the odds of LBW. While residual confounding and biases stemming from missing data are important, the findings provide some certainty that exposure to early nevirapine, and early and late PI do not increase risk for LBW

We found women with mixed ancestry to be associated with LBW which was different to previous US and European studies in which black race has been associated with LBW and preterm birth [28]. There were only eight women of mixed ancestry in this study group and it is possible that they represent a unique group that has not been studied for birth outcomes before. One South African study of women with mixed ancestry in the Cape, showed high infant mortality rates with LBW as a major contributing factor [64].

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HIV has also been associated with LBW and specific risk factors for LBW include low maternal CD4 cell count and advanced clinical stage [48]. Of note, in this cohort, low CD4 cell count emerged as an important risk factor for both LBW and prematurity, with every gain of 50cells/mm^3 being associated with significantly reduced risk of these adverse events.

Women on HAART less than 3 weeks were associated with LBW because the duration of HAART was probably not long enough to impact foetal growth. This group was therefore similar to the HAART-unexposed group and had more SGA infants. Women on HAART more than 30 weeks were associated with LBW due to increased preterm births in this group. This is congruent with our previous finding that duration of HAART in pregnancy is directly related to preterm birth rate.

4.4.2 Variables not associated with LBW

The following variables were not associated with LBW:

- Infant gender
- Smoking
- Alcohol use
- Previous preterm birth
- Previous miscarriage
- Anaemia
- Diabetes
- Syphilis

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Previous studies have identified male gender as a risk for preterm birth and LBW [28]. In our study male and female infants were equally at risk for LBW. Heavy alcohol use has been associated with LBW and preterm birth. In our study very few women used alcohol and the extent of alcohol use was not quantified but it is possible that alcohol use was not heavy enough to affect birth weight. Similarly smoking has been linked to preterm birth and LBW but it is possible that the number of smokers in our study were too few and /or the women did not smoke enough for it to pose a risk [28]. Unlike other studies, previous preterm birth, previous miscarriage, anaemia and syphilis were not associated with LBW but a trend of increased rate of LBW among RPR positive and severely anaemic women was detected [28, 58]. It is possible that there were not enough women with these risk factors in our study to demonstrate these associations.

4.5 LIMITATIONS

Due to the retrospective nature of the study, there were gaps in the data obtained. The ANC ARV program was designed with the primary goal of clinical care, with observational research as a secondary component. Efforts are made to record all pertinent data and ensure follow-up, but data reflect the realities of our practice circumstance, with missing information on women who completed follow-up as well as a large number of women and infants lost to follow-up before infant HIV testing. Reportedly, pregnant women often come to Johannesburg for antenatal care but return to their homes at remote locations for infant delivery and often remain confined to their homes in the early postpartum period. Additionally, women face stigma, poverty, and fear about infant HIV diagnosis, all of which

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may serve as a deterrent to returning for 4-6 week infant testing and results. Linkage of antenatal and HIV services in the ANC-ARV clinic attempts to overcome some of these barriers, but retaining women in care remains a significant challenge. In this analysis we attempted to evaluate the influence of some missing data by performing comparisons among women with and without information on HAART duration. This analysis did not show differences in women who had information on HAART duration versus those that did not.

Substantial gaps in data existed and analysis was restricted to subjects with complete data for each specific variable. This approach could have resulted in information bias and limits the external validity of our results.

Data on the WHO clinical stage was not collected for HAART-unexposed women. This is a limitation of the study because it would have been useful to compare the WHO clinical staging of HAART-exposed versus HAART-unexposed women.

HIV viral load prior to delivery is a useful marker of adherence to HAART regimen and likelihood of transmission of the virus from mother to child [10]. This is not routinely collected in the study hospitals and was therefore not available for inclusion in the analysis.

TB information was only available from JH women, most of these were on NVP-based regimens, and was therefore not a true reflection of the entire study group. Women exposed to early EFV-based HAART had the highest rates of TB because this regimen was used with

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TB co-infection according to JH protocol. Any maternal infection poses a risk for intrauterine growth restriction and/or preterm birth [53, 65] and the incomplete TB data in this study is a limitation.

Body mass index of women was also not available and this could have impacted LBW and preterm birth rate [23, 28].

The study design meant that the group of HAART-unexposed women had received less antenatal care and had poorer health-seeking behaviour than their HAART-exposed counterparts which resulted in selection bias. This could have impacted the higher rate of LBW and SGA infants in the HAART-unexposed group but would not explain their lower rate of preterm births.

The study hospitals served different communities with inherent differences. We attempted to negate some of these confounding factors in our analysis but acknowledge that some may still have impacted the study outcome. JH hospital, where more NVP-based and EFV-based HAART is used, has a more complicated patient base and this could have impacted the rates of preterm birth and LBW in these patients.

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4.6 CLINICAL IMPLICATIONS

HAART has been shown to reduce vertical transmission of HIV and improve maternal morbidity and mortality [3]. It is important to quantify its negative effect on birth outcomes in order to help patients make an informed decision about initiating HAART. Although we found an association between HAART and preterm birth, this risk was small and in this group of immunocompromised women no impact on birth weight was observed probably due to the protective effect of HAART on HIV-related intrauterine growth restriction. These findings should help reassure clinicians and HIV positive pregnant women that HAART is relatively safe in pregnancy.

The morbidity and mortality benefits of initiating HAART before CD4 cell count decline to below 350cells/mm^3 have been shown [66, 67]. A recent study based in South Africa showed that even in resource-limited settings, this approach is cost-effective and beneficial to long-term survival [68]. South Africa has recently followed this recommendation, and safe regimens have to be sought for pregnant women with CD4 cell counts between 250 and 350 cells/mm^3. Currently the South African PMTCT guidelines advocate NVP-based HAART regimens as the first line regimen for pregnant women [40,71]. Women who have contra-indications to NVP due to resistance or adverse reactions are candidates for PI-based regimens. Additionally, NVP-based regimens have been associated with a ten fold increase in hepatic complications in women with CD4 cell counts above 250cells/mm^3 [68, 69]. Concerns about the teratogenicity of exposure to EFV in the first trimester, limits it's use to the second and third trimesters of pregnancy [49]. Concerns about the cost and risk of preterm delivery associated with PI-based regimens have made them less appealing. This

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study suggests that in women with CD4 cell counts below 250cells/mm^3, boosted PI-based regimens do not increase the risk of preterm delivery more than other types of HAART. Further study is necessary to investigate if this is true for pregnant women with CD4 cell counts between 250 and 350cells/mm^3.

Of note, in this cohort, low CD4 cell count emerged as an important risk factor for both LBW and prematurity. This finding highlights the importance of early HIV diagnosis and staging during pregnancy to accelerate HAART initiation in women who qualify. The recent South African guideline change [71] to increase the CD4 cell count treatment threshold to 350 cells/mm^3 may help minimise adverse pregnancy outcomes related to immune compromise. Further study is warranted so that consideration can be given to evaluating even higher CD4 cell count thresholds, as increase in CD4 count is a modifiable factor that could reduce morbidity and mortality for both mothers and newborns.

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CHAPTER 5

5.0 CONCLUSIONS

In this cohort of immunocompromised women HAART-exposure was associated with increased preterm birth between 34 and 37 weeks of gestation and a longer duration of HAART exposure increased this risk. This finding disproved the null hypothesis that HAART-exposure was not associated with preterm birth. Exposure to PI-based regimens was not associated with preterm birth compared to NNRTI-based regimens.

While HAART was associated with preterm birth, it was protective against low birth weight caused by HIV-induced intrauterine growth restriction. Immunocompromised HAART-unexposed women had increased rates of SGA infants compared to their HAART-exposed counterparts.

Low CD4 count emerged as an important modifiable risk factor for both LBW and preterm birth emphasizing the need for urgent HAART in women with low CD4 counts to boost maternal immunity and prevent adverse foetal outcomes.

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These findings contribute to the limited knowledge about antenatal HAART-exposure in the African context. They reassure that the risk for adverse pregnancy outcomes attributable to HAART are small and likely to we outweighed by its protection against maternal and infant morbidity and mortality.

Further study on the ideal gestation to initiate HAART in pregnant women who have no clinical indication for it, early enough to allow viral suppression and minimize mother to child transmission of HIV but late enough to decrease risk of preterm birth, would be useful.

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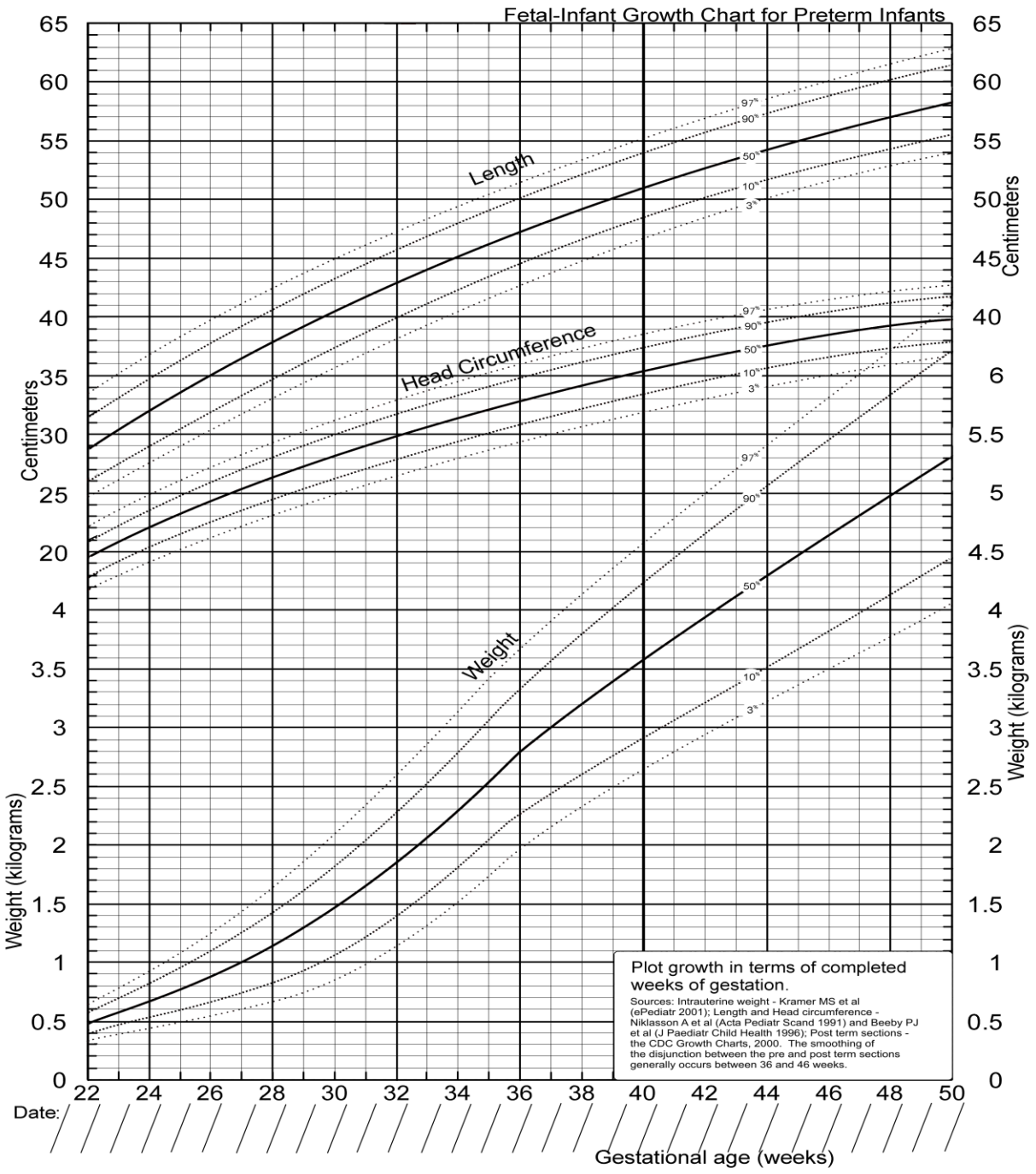
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Appendices

APPENDIX 1



APPENDIX 2

Coronation Women and Children Hospital

CONSENT FORM: USE OF CLINICAL INFORMATION

This document must be explained to the patient/family member/guardian by a member of the clinical staff and a copy of the signed document is to be given to the patient/family member/guardian.

Dear Guardian and Patient,

You/your child are currently attending Coronation Hospital for treatment of problems you/your child are/is currently experiencing. The Hospital not only renders treatment but is also actively involved in conducting research aimed at improving the quality of care we deliver. From time to time such research involves the use of patient records from which information is extracted. The use of such information is subject to:

1 Approval from the Committee for Research on Human Subjects (University of the Witwatersrand)

2 Anonymity i.e. the identity of the patient from whose file information is extracted is never revealed to anyone but the researcher unless specific consent is obtained to do so.

Whilst we are not currently involved in research that requires us to use any information now, this may change in the future when you are already discharged. We would like to obtain your consent to use information from your file for the purpose of research, subject to the aforementioned conditions. If you choose not to give consent, this will not compromise your treatment in any way. If at any time you choose to withdraw consent you are free to do so and will not be prejudiced in any way.
Should you wish to contact us at any stage regarding this consent, contact Coronation Hospital at (011) 470 9424/9207.

PATIENT NAME:…….

A.
I.....hereby give consent for my/my child's records to be used as per the abovementioned conditions for the purposes of research:

GUARDIAN NAME and RELATION:.....

SIGNATURE:…….. DATE:.....

WITNESS:..... DATE:.....

B.
I.....do not give consent for my/my child's records to be used:

GUARDIAN NAME and RELATION:……..

SIGNATURE:..... DATE:.....

WITNESS:..... DATE:.....

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