

The copyright of this thesis rests with the University of Cape Town. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

University of Cape Town

GROWTH OF HIV EXPOSED AND UNEXPOSED INFANTS:

a prospective cohort study in three different settings in South Africa

Student: Vundli Ramokolo
Student number: RMKVUN001

May 2010

A mini dissertation submitted to the University of Cape Town School of Public Health in partial fulfilment of the requirements for a Masters Degree in Public Health (Epidemiology)

ACKNOWLEDGEMENTS

I would love to thank:

Supervisors

Tanya, Debra, and David- Thank you very much for guiding and supporting me from the conception through to the completion of this work. I would also like to thank you for the countless hours you have spent reviewing my work.

Family & friends

Family - Thank you for your support during this season

Shala: Thank you for always believing in me

Friends- Thank you for your encouragement

Selamawit- I treasure your insightful input

Lord Jesus

I really appreciate Your presence in my life. Ububele Bakho buyangigcina ngci.

DECLARATION

UNIVERSITY OF CAPE TOWN

PLAGIARISM

Declaration

1. I know that plagiarism is wrong. Plagiarism is to use another's work and pretend that it is one's own.
2. I have used the ...**HARVARD**..... convention for citation and referencing. Each contribution to, and quotation in, this essay/report/project/..... from the work(s) of other people has been attributed, and has been cited and referenced.
3. This essay/report/project/...**THESIS**..... is my own work.
4. I have not allowed, and will not allow, anyone to copy my work with the intention of passing it off as his or her own work.

Signature: _____

Date: _____



HAND-IN SLIP

CON

CEM Signature:

Lectures Name:

Student Name: **VUNDLI RAMOKOLO**.....

Date:

EXECUTIVE SUMMARY

BACKGROUND AND OBJECTIVES

Malnutrition, which is widespread in many parts of South Africa, is a problem that affects child growth and predisposes children to early death. Another driver of child mortality in South Africa is the HIV/AIDS epidemic. An understanding of the interactions between malnutrition and HIV is therefore important, especially for vulnerable groups such as infants. This study is aimed to report on growth, in the first 36 weeks of life, of infants in three cohorts of mother-infant pairs: those infected by their HIV-positive mothers (infected), HIV-negative infants born to HIV-positive mothers (uninfected), and HIV-negative infants born to HIV-negative mothers (unexposed). Infant growth was also compared between the three different settings in South Africa.

METHODS

A prospective cohort study, called the Good Start Study, was conducted in three different settings in South Africa. Mothers were recruited at 28-36 weeks of pregnancy and followed up until the 36 weeks post delivery. Infant growth measurements were taken at 3, 24 and 36 weeks during scheduled home visits. The work presented in this document was a secondary analysis of data collected during the Good Start Study. Mean z-scores were calculated for length-for-age (LAZ), weight-for-age (WAZ) and weight-for-length (WLZ), and if they were below minus two, the infant was considered as moderately stunted, underweight and wasted, respectively. Mean z-scores, stratified by infant HIV exposure and infection status at three weeks, were plotted against infant age to assess growth over time.

RESULTS

The final sample included 98 infected, 386 uninfected and 193 unexposed infants. Although these infants differed significantly with regard to some demographic characteristics, these differences were minor. Infected infants had significantly lower mean WAZ (-1.11) compared to uninfected (-0.55) and unexposed (-0.55) infants at the three week ($P < 0.01$) and subsequent

visit times ($P < 0.01$). Infected infants had significantly ($P < 0.01$) lower mean WLZ (0.02) than uninfected (0.72) and unexposed (0.52) infants at 24 weeks. Infected infants had a significantly lower mean LAZ (-1.09) compared to uninfected (-0.29) and unexposed (-0.44) infants at 24 week visit ($P < 0.01$), as well as at the 36 week ($P < 0.01$), but not the three week visit ($P = 0.50$). No significant difference ($P > 0.05$) in all mean z-scores was observed between uninfected infants and unexposed infants. Results from the multivariate analysis showed a significant ($P = 0.01$) effect of time on the difference in mean WAZ between uninfected infants and unexposed infants between the 3 and 24 week visit times. Uninfected infants had a steeper growth trajectory compared to unexposed infants. Infants living in Rietvlei were significantly ($P < 0.01$) more stunted compared to infants in the wealthier sites of Umlazi and Paarl.

CONCLUSION

HIV-infected infants in this study were significantly more malnourished compared to uninfected or unexposed infants. The growth of uninfected infants did not differ significantly from that of unexposed infants. Early HIV infection and not exposure placed infants at increased risk of growth failure. Prevention of mother-to-child transmission of HIV and prompt diagnosis of infant infection at around 6 weeks, with appropriate care including assessment for eligibility for ARV's, is critical to prevent malnutrition in HIV-infected children.

CONTENTS

TABLE OF CONTENTS

ABBREVIATIONS	viii
DEFINITIONS.....	ix
CHAPTER 1: INTRODUCTION.....	1
1.1 PROBLEM STATEMENT & STUDY JUSTIFICATION	1
1.2 LITERATURE REVIEW	2
1.3 HYPOTHESIS	16
1.4 AIMS.....	16
1.5 OBJECTIVES.....	16
CHAPTER 2: METHODOLOGY	17
2.1. PRIMARY STUDY: GOOD START STUDY	17
2.2 THESIS SUB-STUDY (SECONDARY DATA ANALYSIS).....	26
CHAPTER 3: RESULTS.....	36
3.1. RESPONSE RATE.....	36
3.2 DATA EXPLORATION	39
3.3 UNIVARIATE AND MULTIVARIATE ANALYSIS OF Z-SCORES BY GROUP.....	45
CHAPTER 4: DISCUSSION.....	60
4.1.1 MATERNAL AND INFANT CHARACTERISTICS.....	60
4.1.2 INFANT GROWTH AND HIV.....	61
4.1.3 FREQUENCY OF MALNUTRITION.....	62
4.1.4 INFANT GROWTH AND SITE	63
4. 2 STRENGTHS OF THIS STUDY.....	64
4.3 STUDY LIMITATIONS	65
4.4 GENERALISABILITY OF RESULTS.....	68
4.5 RECOMMENDATIONS.....	69
4.6 FUTURE RESEARCH.....	71
REFERENCES	73
APPENDICES	77
Appendix a: Ethics Approval for Good Start Study	77
Appendix b: Ethics Approval for secondary study.....	78

LIST OF TABLES

Table 1: Dummy table of mixed effect model	32
Table 2: WHO exclusion range for z-scores (World Health Organization, 1995)	36
Table 3: Distribution of anthropometric data.....	37
Table 4: Participant characteristics by anthropometric data availability.....	37
Table 5: Participant characteristics by site.....	39
Table 6: Analysis of mean LAZ by site	40
Table 7: Analysis of mean WAZ by site.....	41
Table 8: Analysis of mean WLZ by site	42
Table 9: Participant characteristics by group.....	43
Table 10: Proportion of underweight (WAZ < -2) infants by group.....	46
Table 11: Summary statistics of WAZ data by group.....	46
Table 12: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and childhood underweight during the three week and 24 week visit times.....	48
Table 13: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and childhood underweight during the 24 week and 36 week visit times.....	49
Table 14: Proportion of wasted (WLZ < -2) infants by group	51
Table 15: Summary statistics of WLZ data by group.....	51
Table 16: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and wasting during the three week and 24 week visit times	52
Table 17: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and wasting during the 24 week and 36 week visit times	53
Table 18: Proportion of stunted (LAZ < -2) infants by group.....	55
Table 19: Summary statistics of LAZ data by group.....	56
Table 20: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and stunting during the three week and 24 week visit times	57
Table 21: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and stunting during the 24 week and 36 week visit times.....	58

LIST OF FIGURES

Figure 1: UNICEF conceptual framework for the causes of malnutrition	8
Figure 2: Cycle of malnutrition and infection in people living with HIV	10
Figure 3: Cycle of malnutrition, immunity and infection and poverty	15
Figure 4: Data collection schematic diagram.....	21
Figure 5: Infant being weighed during a home visit in the Good Start Study	22
Figure 6: Infant length measurement taken during a home visit in the Good Start Study.....	23
Figure 7: Different intercepts for different groups	32
Figure 8: Different gradients for different groups	33
Figure 9: Box and Whisker plot of gestational age	38
Figure 10: Box and Whisker plot of number of live births	38
Figure 11: Childhood underweight mean z-scores versus visit time.....	50
Figure 12: Wasting mean z-scores versus visit time	54
Figure 13: Stunting mean z-scores versus visit time.....	59

ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
ANC: Antenatal care Clinic
ANOVA: Analysis of Variance
ARV: Anti Retroviral
CD4: Cluster of differentiation four
Child PIP: Child Healthcare Problem Identification Programme
CHW: Community Health Worker
HAART: Highly Active Anti-Retroviral Treatment
HIV: Human Immunodeficiency Virus
INP: Integrated Nutritional Programme
LAZ: Length-for-age z-score
Lcl: Lower confidence limit
MDG: Millennium Development Goal
MTCT: Mother-To-Child Transmission
NDoH: National Department of Health
PLHIV: People Living with HIV
PMTCT: Prevention of Mother-To-Child Transmission
PPP: Purchasing Power Parity
SAVACG: South African Vitamin A Consultative Group
SD: Standard Deviation
SOP: Standard Operating Procedures
TALC: Teaching Aids at Low Cost
Ucl: upper confidence limit
UNAIDS: Joint United Nations Programme on HIV/AIDS
UNICEF: United Nations Children's Fund
VCT: Voluntary Counselling and Testing
WAZ: Weight-for-age z-score
WHO: World Health Organisation
WLZ: Weight-for-length z-score

DEFINITIONS

Early Postnatal Transmission: Postnatal vertical transmission before 3 weeks of age

EBF: Feeding only breast milk, without any complementary liquid or solid foods (except medicines ordered by medical doctors)

EFF: Feeding infant's only formula milk

Infected infants: HIV infected infants born to HIV positive mothers

MBF: Feeding infants with breast milk in addition to other solids and liquids

MFF: Feeding infants formula milk with additional solids and liquids, but not breast milk

Stunting: Length-for-age z-score less than - 2.0

Underweight: Weight-for-age z-score less than - 2.0

Unexposed infants: HIV-negative infants born to HIV-negative mothers

Uninfected infants: HIV-negative infants born to HIV-positive mothers

Wasting: Weight-for-length z-score less than - 2.0

University Of Cape Town

CHAPTER 1: INTRODUCTION

1.1 PROBLEM STATEMENT & STUDY JUSTIFICATION

- Malnutrition affects child growth and predisposes children to premature death. It has a synergistic role in diarrhoea, acute lower respiratory infections and other infectious diseases and contributes to the burden of low birth weight (Bradshaw et al., 2003, Sanders et al., 2007) . Child malnutrition is prevalent in many parts of South Africa, despite efforts by the government, non-governmental Organisations and other interest groups. The prevalence of malnutrition, especially stunting, varies according to socio-economic status (SES). The 2005 National Food Consumption Survey reported less stunting in urban (16.00%) compared to rural (20.00%) children in South Africa (Labadarios, 2008) . Malnutrition is a complex phenomenon with numerous risk factors. These risk factors vary between and within countries. The devastating effect of the HIV epidemic on the health of the nation has made this disease one of the leading risks for poor health in South Africa. There is, therefore, a need for research on the association between HIV and malnutrition, especially in vulnerable groups such as women and children. Findings from studies done in some African countries indicate that HIV infection impairs early childhood growth. These studies assessed child growth cross-sectionally, at different points in time. Based on the premise that infant growth is a time-dependent phenomenon, this current study went a step further and assessed the longitudinal relationship between infant growth and HIV exposure and/or infection.

1.2 LITERATURE REVIEW

It is estimated that 14 million children in Europe were overweight in 2004. Three million of these children suffered from obesity (The Lancet, 2006) . While many developed countries have a high burden of lifestyle diseases such as obesity in children, numerous low-to-middle-income countries still struggle to adequately feed their young. Diseases of deprivation such as low birth weight (birth weight below 2500g), diarrhoeal diseases and acute lower respiratory infections (pneumonia, bronchiolitis and bronchitis) remain widespread in these low-to-middle-income countries. The latest regional estimates of low birth weight range from 6.00% in the East Asian and Pacific region to 27.00% in the South Asian region. The percentage of infants with low birth weight is estimated to be 15.00% in the Sub-Saharan African region (UNICEF, 2009). Diarrhoea and acute lower respiratory infections are estimated to have accounted for between 15.00% and 18.00% of child deaths, respectively, in developing countries in 2002(UNICEF, 2004).

Malnutrition, which refers to both under-nutrition and over-nutrition, is also rampant in developing countries. Under-nutrition involves both protein-energy malnutrition and micronutrient (iron, zinc, vitamin A and iodine) deficiencies. Over-nutrition is the excessive intake of energy and/or macronutrients(Faber and Wenhold, 2007). Malnutrition can also arise due to the consumption of food with inadequate nutrients, calories and protein, for growth and maintenance, and when individuals have decreased intake or are not able to absorb and metabolise food because of infections such as diarrhoea (secondary malnutrition)(World Health Organization, 2008) .

Poor growth in infants and children is one of the first signs of nutrition deprivation. Anthropometry, which compares the growth measurements of the child against that of a healthy reference population, can be used to evaluate the nutritional status of the child. The extent of malnutrition in a population can also be assessed by dietary, biochemical and clinical methods.

1.2.1 MEASURING MALNUTRITION

Anthropometry is commonly used to assess malnutrition because it is not only an objective measure of malnutrition but is also non-invasive and more cost-effective compared to expensive biochemical methods. The key variables used in anthropometry are age, sex, height and weight providing weight-for-age (WAZ), length-for-age (LAZ) or height-for-age (HAZ) and weight-for-length (WLZ) or weight-for-height (WHZ) measures. These indices classify different nutrition related conditions in infants and children(Cogill, 2003).

- **Low WAZ** indicates underweight for that specific age. This index reflects both stunting (chronic malnutrition) and/or wasting (acute malnutrition) but does not distinguish between the two. It can therefore be used to capture changes in the magnitude of malnutrition over time(Cogill, 2003).
- **Low HAZ** (for children above 2 years of age) and **low length-for-age** (for children below 2 years of age) are good measures of past or chronic malnutrition. They however cannot measure short-term effects of malnutrition. A child with a low HAZ is stunted for that specific age group and this is a sign of past growth failure(Cogill, 2003).
- **Low WHZ** (for children above 2 years of age) and **low WLZ** (for children younger than 2 years of age) identify acute malnutrition or wasting which often results from seasonal shortages of food in households(Cogill, 2003).

1.2.2 GLOBAL MALNUTRITION

Malnutrition is the primary cause of death in 50.00% of children under five years of age. In 2006 approximately 9.7 million children died before their fifth birthday(UNICEF, 2007). The global prevalence of childhood underweight is projected to decline by 34.00% (95%CI= -43.00%; -23.00%), from 27.00% in 1990 to 18.00% in 2015. The same trend is expected in developing regions where childhood underweight is estimated to decrease by 36.00% (95% CI= -45.00%; -

26.00%) from 30.00% to 19.00%. In Africa however, prevalence of childhood underweight is forecasted to increase by 12.00% (95% CI= 8.00%; 16.00%), from 24.00% in 1990 to 26.00% in 2015(De Onis et al., 2004).

In 2005, about 20.00% of children living in developing countries were moderately underweight and 32.00% were stunted. The majority of these children lived in Africa and Asia. The Southern African sub-region had 30.00% of its child population being stunted and 11.00% were underweight (Black et al., 2008).

Poor anthropometric outcomes were also prominent in the eastern African sub-region. Half (24.40 million) of the child population was stunted while 28.00% was underweight (Black et al., 2008).

The south-central Asian sub-region was one of the worst areas with 33.00% of its population of children under 5 years of age being moderately underweight and 41.00% were stunted. India, situated in that sub-region, had about 51.00% of its child population being stunted. This translates to 34.00% of the global prevalence for stunting and is a cause for concern (Black et al., 2008).

Wasting was less prevalent in comparison to stunting and underweight as only 10.00% of children were wasted globally. Yet again, the south-central Asian sub-region was one of the most affected areas. The prevalence of wasting was estimated to be 16.00% in that sub-region and this was the highest globally (Black et al., 2008).

1.2.3 MILLENNIUM DEVELOPMENT GOALS

The effects of poverty on human health are devastating, and the global community committed itself to reducing extreme hunger and poverty in the Millennium Declaration. The Declaration included eight Millennium Development Goals (MDGs) and 16 targets that address poverty reduction, access to education, gender equality, health and environmental sustainability. This Millennium Declaration was endorsed by 189 countries, including South Africa, in September 2000 (United Nations, 2000).

MDG one, which has two measurable targets, focuses on the eradication of extreme poverty and hunger. The first target focuses on halving the proportion of people whose income is less than one dollar a day between 1990 and 2015. Progress towards achieving this target is monitored by looking at the 1) proportion of the population whose income is below \$1 purchasing power parity (PPP) per day, 2) the poverty gap ratio [incidence x depth of poverty] and 3) the share of poorest quintile in national consumption. The second target is to halve, between 1990 and 2015, the proportion of people who suffer from hunger. Indicator four and five, which measure the prevalence of underweight children under five years of age and the proportion of the population below minimum level of dietary energy consumption, respectively, are used to monitor progress towards this target (United Nations, 2000).

The 2005 South African MDGs country progress report indicated that the proportion of the population that is living below the international poverty line of US\$1 per day was 7.60% while the proportion of the population living below international poverty line of US\$2 per day was 30.90%. The Gini-coefficient measures the level of income inequality in a society. It varies between 0 and 1 with the lower numbers (0.0-0.40) being most desirable as they represent a more equal distribution of income within a society. The closer to 1 the Gini coefficient is, the more unequal the distribution of income is in that society (World Bank, 2009). The Gini-coefficient was 0.69 in South Africa in 2006, indicating an unequal distribution of income in the society. The overall increase in this coefficient between 1993 and 2006 indicates that the gap between the rich and the poor is still widening (Government of South Africa and United Nations, 2005)

1.2.4 MALNUTRITION IN SUB-SAHARAN AFRICA

More than 33.00% of child deaths are attributable to maternal and child under-nutrition in the sub-Saharan African region (UNICEF, 2007). This region was forecasted to experience an increase in the number of underweight children. Chopra and Darnton-Hill (2006) and de Onis (2004) forecasted that the prevalence of childhood underweight will increase by 9.00% from 26.80% in 1990 to 29.20% in 2015.

Poor anthropometric outcomes are still prevalent in the sub-Saharan region. About 28.00% of children under five years of age, living in this region, were underweight between 2000 and 2006 (UNICEF, 2007). The Southern African sub-region had 23.00% of its children being underweight (UNICEF, 2007).

Stunting was the most prevalent anthropometric outcome in the sub-Saharan African region indicating that chronic malnutrition was a serious problem in this region. The Southern African sub-region had a prevalence of 41.00% between 2000 and 2006 (UNICEF, 2007).

Wasting was the least prevalent anthropometric outcome in sub-Saharan Africa between 2000 and 2006. The prevalence was least (6.00%) in the Southern African sub-region. (UNICEF, 2007).

1.2.5 MALNUTRITION IN SOUTH AFRICA

Malnutrition is on a rise in the Sub-Saharan region and in South Africa. Thirty percent of child deaths in South Africa are attributed to malnutrition (Bradshaw et al., 2003). The increase in malnutrition in South Africa is strongly associated with the HIV/AIDS pandemic (Academy of Science of South Africa, 2007).

1.2.5.1 ANTHROPOMETRIC STATUS OF SOUTH AFRICAN CHILDREN

The latest National Food Consumption Survey estimated that 18.00% of South African children aged 1-9 years are affected by stunting. Wasting and underweight affect one in twenty and one in ten South African children, respectively (Labadarios, 2008). Stunting is the most common form of malnutrition in South African children.

Anthropometric outcomes in children vary between the nine provinces in South Africa. Wasting, in children aged 6-71 months, ranges from 0.70% in Kwa-Zulu Natal to 3.50% in the Limpopo province. The proportion of stunted children aged between 6 and 71 months ranges from 11.50% in Gauteng to 34.20% in Limpopo. Childhood underweight in females ranges from 3.00% in Kwa-Zulu Natal to 12.20%

in the Northern Cape. It ranges from 3.90% in Kwa-Zulu Natal to 25.70% in the Northern Cape in males of the same age group (Day and Gray, 2007). According to the 2005 National Food Consumption Survey, children living in urban settings are the least (16.00%) affected by stunting. The prevalence stunting varies within these urban settings with children living in informal urban areas (18.50%) being more affected by stunting compared to those living in formal urban areas (15.60%) (Labadarios, 2008). In rural areas, stunting was more pronounced in children (aged 1- 8.9 years) living on commercial farms, according to results from the 1999 National Food Consumption Survey. Childhood underweight was more prevalent in children (aged 1- 3 years) living in rural areas, especially those on commercial farms, compared to urban areas. Wasting, on the other hand, was most pronounced in children living in urban areas (Steyn et al., 2005)

1.2.5.2 MICRONUTRIENT DEFICIENCIES: THE HIDDEN HUNGER

Hidden hunger, a phenomenon that describes an individual who is deficient of one or more micronutrients, has a synergistic relationship with infection (Academy of Science of South Africa, 2007). A child suffering from hidden hunger is seldom deficient in only one micronutrient. In most cases a child is deficient in two or more micronutrients which further compromises immune function (Faber and Wenhold, 2007).

1.2.6 DETERMINANTS OF MALNUTRITION

In 1990, UNICEF proposed a strategy for addressing child malnutrition in developing countries. The two major components of this strategy were 1) a method of assessment, analysis and action and 2) a conceptual framework for assessing the determinants of malnutrition in a specific setting (UNICEF, 1998)

The South African Government has a number of programmes that are concerned with the eradication of malnutrition. A new and more comprehensive, compared to the previous fragmented food-based programmes, Integrated Nutritional Programme (INP) was established in 1997. The INP is partly based on 1) the UNICEF conceptual framework of the causes of malnutrition and 2) their triple A approach of

accessing a problem such as malnutrition, analyzing its causes and taking action based on the analysis (National Department of Health, 2009).

Malnutrition is a very complex phenomenon with many causes (see Figure 1). The United Nations has divided these causes into three main groups, namely, immediate, underlying and basic causes of malnutrition.

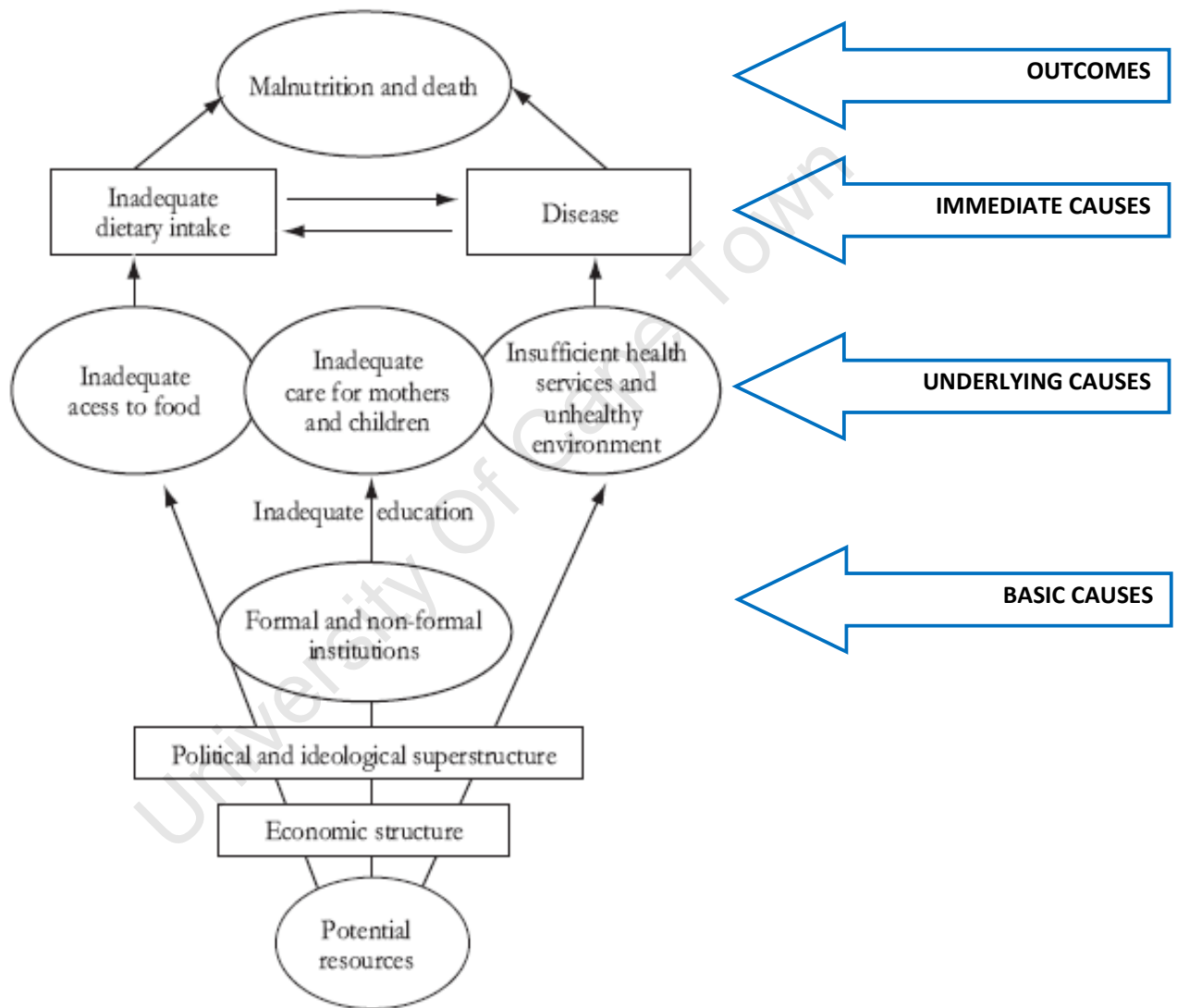


Figure 1: UNICEF conceptual framework for the causes of malnutrition

1.2.6.1 IMMEDIATE CAUSE OF MALNUTRITION

The two immediate causes of malnutrition, which operate at the individual level, are inadequate food intake and infection (UNICEF, 1998). Malnutrition has a synergistic interaction with infections. Therefore, the combined effect of malnutrition and infection is more intense compared to the sum of the effects of malnutrition and infection alone (Scrimshaw et al., 1968). Malnutrition, especially generalised protein energy malnutrition (PEM), makes one more susceptible to infections because it interferes with several defence mechanisms such as the production of antibodies, cell mediated immunity and non-specific defence mechanisms (Scrimshaw and SanGiovanni, 1997). PEM also causes atrophy of lymphoid tissue (especially around the T-lymphocyte areas) and this is particularly seen in children. This reduces the blood counts of lymphocytes and eosinophils. The various immunological dysfunctions resulting from malnutrition are collectively termed Nutritionally Acquired Immune Deficiency Syndrome (NAIDS) (Beisel, 1996).

Infections, on the other hand, can lead to malnutrition. For example: 1) gastrointestinal infections can cause severe diarrhoea leading to nutrient deficiency, 2) parasitic infections such as tape worms can cause anaemia and 3) infectious diseases such as HIV/AIDS and tuberculosis can cause nutrient deficiencies (Schaible and Kaufmann, 2007). In a study done in Nigeria, measles-infected children had significantly ($P < 0.001$) reduced serum levels of essential amino acids compared to uninfected children (Phillips et al., 2004). In response to infection by diseases such as measles, the body elicits innate and acquired host immune responses. These mechanisms increase the body's anabolic energy demand and this subsequently leads to weight loss and malnutrition (Schaible and Kaufmann, 2007).

Thus malnutrition, immunity and infections are all involved in a vicious cycle. Malnutrition interferes with the immune system and leads to ineffective immunity. A compromised immune system results in an increased susceptibility to infections. Infections increase the body's energy consumption as several energy requiring immune responses are triggered. This subsequently leads to weight loss, energy loss, nutrient deficiency and an overall deteriorating health condition (Scrimshaw et

al., 1968). The vicious cycle between malnutrition, immunity and infection has also been explored in people living with HIV (PLHIV). As seen in Figure 2, poor nutrition in the HIV positive individual compromises the immune system's ability to control the HIV infection. A compromised immune system makes one more susceptible to secondary infections which then quickens the progression to AIDS. Infections result in a number of immunological dysfunctions which worsen the nutritional status of the individual and these include; 1) the lack of appetite which reduces food intake, 2) malabsorption of nutrients due to conditions such as diarrhoea and 3) an increase in energy demand due to an upsurge of energy-requiring defence mechanisms (Family Health International., 2007).

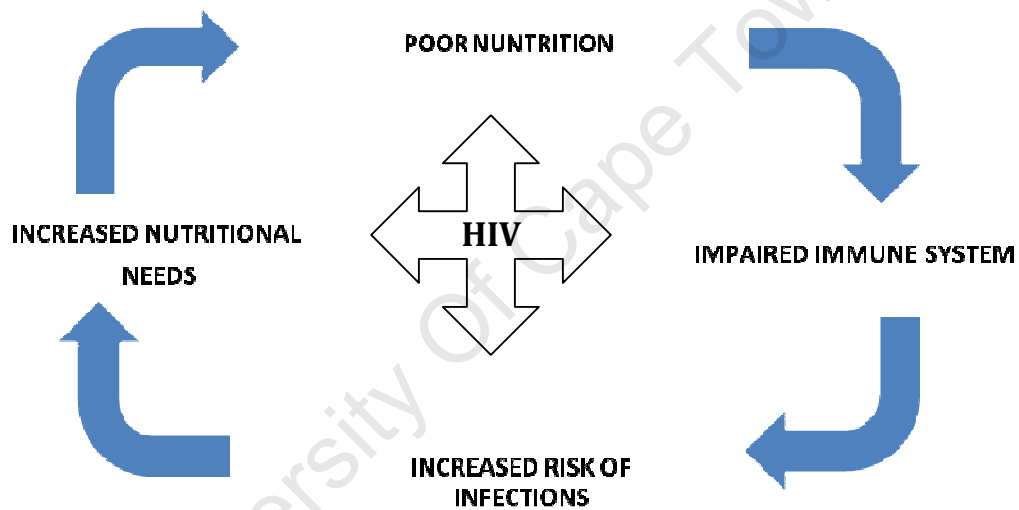


Figure 2: Cycle of malnutrition and infection in people living with HIV (adapted from Family Health International, 2007)

1.2.6.1.1 HIV AND MALNUTRITION

HIV/AIDS infections account for approximately 57% of deaths in children and more than 80% of deaths after 28 days and before 5 years of age in South Africa (Chopra et al., 2009). Isanaka et al. (2009) reviewed fifteen studies that evaluated the association between HIV/AIDS infection and infant growth in developing countries. A few of these studies are discussed below. Most have reported impairment in the

growth of HIV-infected children early in life. Results from a Ugandan based cohort study showed significantly ($p < 0.05$) lower WHZ, LAZ and WAZ in HIV infected infants born to HIV-infected mothers (HIV-infected infants) compared to HIV-uninfected infants born to HIV-uninfected mothers (HIV-uninfected infants) (Bakaki et al., 2001). Lepage et al. (1996) observed consistently lower z-scores for LAZ and WAZ in HIV-infected Rwandan infants compared to their HIV-uninfected counterparts. The WLZ of HIV-infected infants were not consistently lower than those of HIV-uninfected infants. These results support those reported by Bobat et al. (2001) in a South African based cohort study. No significant difference in the mean z-scores for WLZ was reported between HIV-infected infants and HIV-uninfected infants. Early and sustained low mean z-scores for LAZ and WAZ were observed in HIV-infected infants, even after adjusting for lower gestational age.

A prospective cohort study in Kinshasa, Democratic Republic of Congo, compared the growth of HIV-infected infants with that of HIV-uninfected infants and HIV-uninfected infants born to HIV-uninfected mothers (unexposed infants). The study was undertaken during a period when ARV treatment was not available. In addition, the extent to which growth failure in HIV-infected infants was: a) a direct consequence of maternal HIV disease progression, b) a consequence of maternal socio-economic conditions, c) secondary to HIV-related clinical illnesses in the infant and d) a function of the infant's environment, is still uncertain in developing countries (Bailey et al., 1999). The aim of the study was therefore to assess infant growth according to maternal immunological and socio-demographic factors in a developing country. Multivariate analysis showed significant association between stunting and HIV-infection in the infant (RR= 2.38, 95% CI= 1.58-3.57) and with prolonged diarrhoea (RR= 1.60, 95% CI= 1.08-2.38). Childhood underweight was significantly associated with HIV-infection in the infant (RR= 2.54, 95% CI= 1.66-3.89), adenopathy (RR= 1.68, 95% CI= 1.15-2.47), severe immune suppression (RR=2.75, 95% CI= 1.36-5.58), prolonged fever (RR=2.11, 95% CI= 1.12-3.98) and male gender (RR= 1.40, 95% CI= 1.05-1.87). Both infant HIV-infection (RR=3.32, 95% CI= 1.96-5.61) and presence of adenopathy (RR=2.26, 95% CI= 1.34-3.83) were predictors of wasting. Thus HIV-infection and HIV-associated illnesses were risk factors for poor anthropometric outcomes (Bailey et al., 1999). Regression analysis showed an odds of falling below minus two z-scores by 20 months for LAZ,

WAZ and WLZ for HIV-infected infants compared to uninfected infants of 2.10, 2.84 and 2.56 respectively. No maternal variables (age, place and type of residence, marital status, material possessions, CD4 count and WHO HIV stage), except maternal stature, were associated with infant growth retardation. Bettylou et al. (2000) found no significant difference in maternal socio-demographic variables, child care, hygiene practices, child feeding practices and child growth indices was reported between HIV-infected infants and HIV-uninfected infants in a study they did in Nairobi, Kenya. They also reported no significant difference in the growth pattern of HIV-infected infants and HIV-uninfected infants. Linear growth retardation in HIV-infected infants has been shown to be associated with viral load (Pollock et al., 1997). An increase in the viral load of HIV-infected infants corresponds to a decline in linear growth, but not in weight. Growth faltering among HIV-infected children has also been shown to be age-dependent. Childhood underweight was more pronounced between 12 and 36 months of age in a cohort of HIV-infected Rwandan children. Stunting was most prevalent after 9 months of age (Lepage et al., 1996).

Infant growth has also been explored by maternal HIV infection status. Masaka et al. (2007) compared the growth of infants born to HIV-infected mothers (HIV-exposed infants) against that of infants born to HIV-uninfected mothers (HIV-unexposed infants) in a Zambian based cohort study. Infant HIV status was not assessed due to ethical reasons. Results showed significantly ($p=0.04$) lower z-scores for WAZ and LAZ in HIV-exposed infants compared to HIV-unexposed infants at 6 weeks postpartum. No significant difference in WLZ was observed between the infant groups. Patel et al. (2010) compared the growth of HIV-uninfected infants against that of a reference group of HIV-unexposed infants. These infants were part of the Vertical Transmission Study (VTS), a cohort study that took place between 2001 and 2004 in the Kwa-Zulu Natal region of South Africa. Results from this study showed no significant difference in growth between HIV-uninfected infants and HIV-unexposed infants. WAZ of the HIV-infected infants were below those of the reference group.

1.2.6.2 UNDERLYING CAUSES OF MALNUTRITION

The underlying causes of malnutrition operate at the household or family level. They are divided into the following three subgroups: inadequate access to food; inadequate care for mothers and children; insufficient health services and unhealthy environment. These causes lead to inadequate food intake and infection (UNICEF, 1998) .

1.2.6.2.1 INADEQUATE ACCESS TO FOOD

UNICEF defines household food security as the sustainable access to safe and sufficient (in quality and quantity) food so as to ensure an adequate intake of food for a healthy life, for all members of the household (UNICEF, 1998). Household food security depends on the accessibility of food rather than the availability of food. Food needs to be consistently accessible, both financially and physically, in order for a family to have food security (UNICEF, 1998).

1.2.6.2.2 INSUFFICIENT HEALTHCARE SERVICES AND AN UNHEALTHY ENVIRONMENT

Preventative and curative healthcare services are essential in reducing the incidence and prevalence of diseases which lead to malnutrition. Access to these healthcare services is therefore important. In terms of curative care, factors such as user fees and lack of transport to healthcare facilities often deter people from seeking healthcare. Preventative care addresses several environmental issues that predispose people to infections, diarrhoea and ultimately malnutrition. These include poor sanitary conditions, lack of access to safe drinking water and the unhygienic handling of food (UNICEF, 1998).

1.2.6.2.3 INADEQUATE CARE TO MOTHERS AND INFANTS

In terms of nutrition, care takes into consideration all the household behaviours that bring about optimum child growth and development using the available food and

healthcare services. These caring behaviours include appropriate feeding practices, support for the mother, cognitive stimulation for the child and protecting the child's health through preventative measures such as immunization (UNICEF, 1998). Poor infant weaning practices (OR 3.0, 95%CI 2.0-4.6) and parental death (OR 38.8, 95%CI 3.8-385.3) were found to be risk factors for severe malnutrition, in a case control study that took place in the Bushbuckridge District of South Africa. Factors such as the child support grant (OR 0.44, 95%CI 0.20-0.97) and a diverse intake of food (OR 0.53, 95%CI 0.41-0.67) were protective against severe malnutrition (Saloojee and De Maayer, 2007).

1.2.6.3 BASIC CAUSES OF MALNUTRITION

Basic causes of malnutrition operate at the societal level. Cultural, economic, political and legal factors affect the extent to which a household can provide adequate nutrition and care for its children (UNICEF, 1998)

1.2.6.3.1 MALNUTRITION AND SOCIO-ECONOMIC FACTORS

The synergism between malnutrition, particularly stunting, and infection is associated with SES factors and most commonly occurs among poorer communities (Taylor, 1983). Proxy indicators of SES such as ownership of an indoor flush toilet, a television and maternal education were found to be predictors of stunting in a cohort of 1 year old Filipino infants (Jones et al., 2008)

Zere and McIntyre (2003) found stunting to be the most prevalent form of malnutrition in a sample of 8848 South African households. This evidence is supported by the 2005 National Food Consumption Survey which also reported that stunting as the most common form of malnutrition in South African children. Zere and McIntyre (2003) also reported an inequitable distribution of stunting within the country. The Eastern Cape and Northern Province, which are amongst the poorest provinces in South Africa, had higher rates of stunting compared to other provinces.

In their paper, (Schaible and Kaufmann, 2007) describe the downward spiral of malnutrition, infection, diseases and poverty. As illustrated in Figure 3, diseases result in an energy loss in the individual which leads to a decline in productivity and development at the community level (Schaible and Kaufmann, 2007) . Populations with a high burden of infectious diseases, such as malaria, are more likely to lack the physical capacity to engage in agricultural and industrial labour (Scrimshaw et al., 1968). The inability to secure employment in these sectors has dire consequences for poor, illiterate communities that cannot enter the formal job sector. The lack of employment in these communities leads to more poverty and malnutrition which spirals back to an increase in disease (Schaible and Kaufmann, 2007).

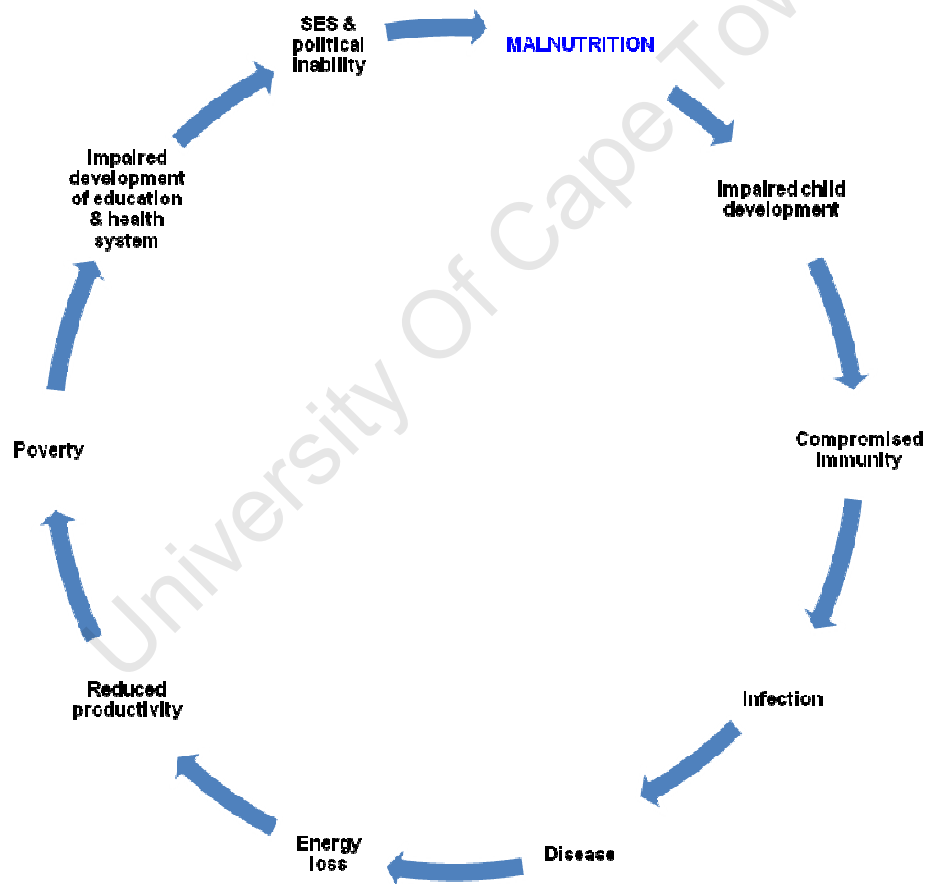


Figure 3: Cycle of malnutrition, immunity and infection and poverty (Adapted from Schaible and Kaufmann, 2007)

1.3 HYPOTHESIS

This study aimed to test the hypothesis that infants with early (3 weeks) HIV-infection have poorer growth in the first 36 weeks of life compared to uninfected infants (born to HIV positive mothers but remain negative) as well as unexposed infants (born to HIV-negative mothers). Infant growth was also expected to differ between three different settings in South Africa namely Paarl, Rietvlei and Umlazi. Infants from more impoverished households were also expected to have poorer growth outcomes compared to infants from more well-to-do households.

1.4 AIMS

The aims of this study were:

- To compare growth, in the first 36 weeks of life, of infants in three cohorts of mother-infant pairs: those infected by their HIV positive mothers (infected), HIV-negative infants born to HIV-positive mothers (uninfected), and HIV-negative infants born to HIV-negative mothers (unexposed)
- To compare the anthropometric outcomes of infants living in three different settings

1.5 OBJECTIVES

The objectives were:

- To compare the anthropometric outcomes of infected infants with those of uninfected infants and unexposed infants, keeping other variables constant
- To report on the frequency of stunting, wasting and childhood underweight in three cohorts: infected infants, uninfected infants and unexposed infants
- To compare the anthropometric outcomes of infants living in Paarl, Rietvlei and Umlazi, while keeping other variables constant

CHAPTER 2: METHODOLOGY

This current study is a secondary analysis of data collected during the Good Start Study. It reports on infant growth up to 36 weeks of age in three cohorts with: HIV-infected infants born to HIV-positive mothers (infected), HIV-negative infants born to HIV-positive mothers (uninfected), and infants born to HIV-negative mothers (unexposed).

2.1. PRIMARY STUDY: GOOD START STUDY

In 2001, a National PMTCT Programme was launched in 18 pilot sites in South Africa. A prospective cohort study was commissioned in 2002 by the National Department of Health to assess the operational effectiveness, as measured by HIV-free survival at 36 weeks post-delivery, of this programme. This prospective cohort study, called the Good Start Study, was conducted in three of the 18 pilot sites namely Paarl, Rietvlei and Umlazi. The study sites are described in detail below. The primary outcomes were infant death and HIV transmission from mother to child by 36 weeks postpartum (Jackson et al., 2007b)

2.1.1 STUDY SITES

The study sites were purposively selected to evaluate PMTCT programme effectiveness in three South African areas with different socio-economic circumstances and antenatal HIV prevalence rates (Jackson et al., 2007b). Paarl, in the Western Cape Province, is a peri-urban/rural area situated 60 km from Cape Town in the heart of the Cape Winelands district. All deliveries are done at Paarl Regional Hospital. This area was selected because it had a well resourced PMTCT programme at the time of the study and was therefore likely to demonstrate good programme effectiveness. The antenatal HIV sero-prevalence in the area was 9.00% in 2004 (Barron et al., 2005). Rietvlei is a rural area situated in the Umzimkulu sub-district within the Alfred Nzo district, one of the poorest districts in South Africa.

At the time of the study Alfred Nzo was part of the Eastern Cape Province; it is now part of Kwa-Zulu Natal province. A community survey in 2001 in the neighbouring Mount Frere district showed that 40.00% of mothers delivered their last child at home(The EQUITY Project, 2001). The antenatal HIV prevalence in the Rietvlei area was 28.00% in 2004(Barron et al., 2005). Rietvlei was chosen to evaluate the effectiveness of the PMTCT programme in a poor rural area with a high HIV prevalence. Umlazi, in the Kwa-Zulu Natal Province, is a peri-urban formal township with both formal and informal settlements situated 20 km southwest of Durban in the Durban-eThekweni district. There is one regional hospital, Prince Mshiyeni Memorial Hospital, which serves as a referral hospital for the surrounding feeder clinics. Delivery services are available at the hospital. The antenatal HIV prevalence in the Umlazi area was 47.00% in 2004(Barron et al., 2005).

2.1.2 STUDY DESIGN

A prospective cohort design was used to collect data. This design was appropriate for collecting data on HIV transmission rates, infant deaths, malnutrition, infant feeding practices, etc.

2.1.3 SAMPLING

2.1.3.1 COMMUNITY AWARENESS

Community health workers (CHWs) and field researchers informed local communities (both residents and leaders) about the Good Start Study. Study flyers were also distributed in the communities (Good Start Study Group, 2002).

2.1.3.2 SENSITISATION AT LOCAL HEALTH FACILITIES

Pregnant women who attended ANC and VCT counselling in the selected local healthcare facilities were given verbal information about the study. These women were also given the study flyers (Good Start Study Group, 2002).

2.1.3.3 PARTICIPANT RECRUITMENT

Field researchers recruited eligible women at the respective local hospital or clinic offering the PMTCT programme. Recruitment either took place antenatally (between 34-36 weeks) at the ANC clinics or postnatally at the postpartum hospital wards. This recruitment took place between 2002 and 2003 and women were recruited every day (Monday- Friday) of the week (Good Start Study Group, 2002).

2.1.3.4 INCLUSION CRITERIA

Consecutive women receiving antenatal care at the three study sites (that had undergone antenatal VCT and tested HIV positive) were recruited for the primary study. These women were only included in the study if they had signed the informed consent form and both mother and infant were alive on discharge from delivery facility. For every three HIV-positive women identified during routine ANC/PMTCT services, one HIV-negative woman was recruited as a control. This control group of HIV-negative women was recruited to: 1) allow for comparisons between HIV-positive and negative women, and 2) to provide an estimate of baseline community infant feeding patterns in the absence of HIV (Good Start Study Group, 2002).

2.1.3.5 EXCLUSION CRITERIA

Participants were excluded if:

- 1) The mother had not signed the informed consent form,
- 2) The mother and/or infant were not alive on discharge from delivery facility,
- 3) The infant was born with congenital malformations, or

4) the woman was deemed not mentally competent to provide adequate informed consent (Good Start Study Group, 2002)

2.1.3.6 STUDY PARTICIPANT RETENTION

Every attempt was made to aid the ability to follow up. During the postpartum interviews, participants provided detailed directions to their homes. This information was used by CHWs to locate and follow-up the participants in their respective communities. Participants that moved from one area to another, within the study catchment area, were transferred to the CHW working in that area. A participant loss form was only completed when a participant; 1) moved out of the study area, 2) was lost to follow-up, or 3) died.

Women that participated in this study were compensated for their participation in the study and this compensation was based on local norms. The participants were given food vouchers, cash vouchers and food parcels to the value of R40.00 (Rands) in all site areas.

2.1.3.7 DATA COLLECTION

- Data was collected between October 2002 and November 2004. HIV positive and negative pregnant women (and their infants) were followed up until 36 weeks post-delivery. Semi-structured interviews in the participants' preferred language (Xhosa, Zulu, Afrikaans or English) were used to collect data at the participants' homes. Data was collected during home visits by a field researcher (at 3, 24 and 36 weeks post-delivery) and by a CHW (at 5, 7, 9, 12, 16, 20, 28 and 32 weeks post-delivery). This data collection schedule is illustrated in Figure 4. The CHWs collected information on infant diet, infant health and on visits to the health facilities (Good Start Study Group, 2002). The field researchers collected data on the following: health care seeking behaviour (both formal and traditional), infant feeding practices during the previous four days, influences on decisions around infant feeding choices, child care practices, maternal and infant morbidity, socio-demographic profile, matters related to disclosure and family support. They also extracted data on

infant birth weight, antenatal, intrapartum and postpartum care, PMTCT programme care, gestational age and newborn complications from the perinatal medical records of the mother and infant at the hospital. In the health facilities abdominal palpation, together with information on the mother's recollection of her last menstrual period, was used to inform the gestational age estimation.

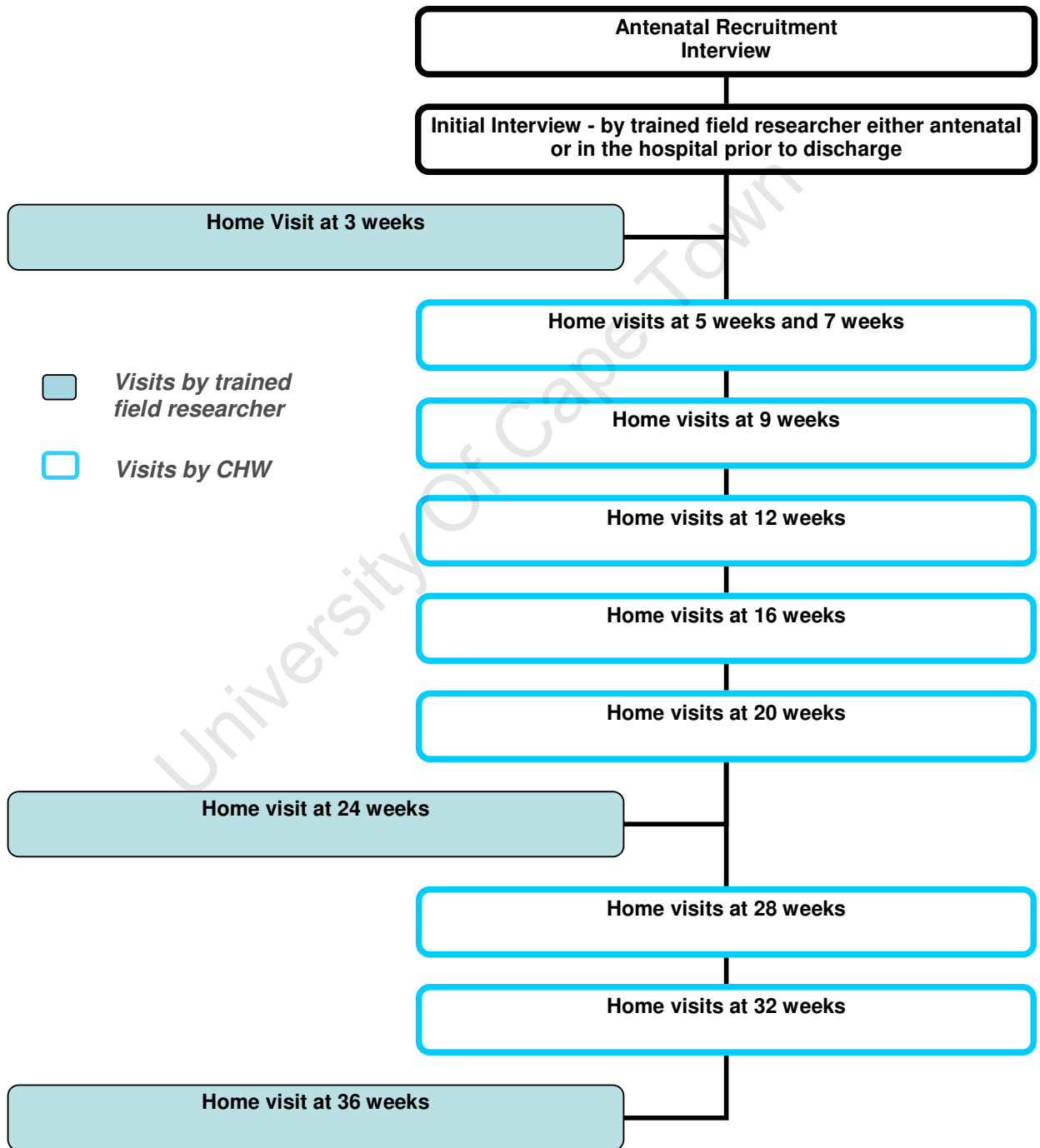


Figure 4: Data collection schematic diagram

Infants were also assessed for weight and recumbent length measurements during the field researcher home visits. All sites used the same scales and length boards. The scales were calibrated with a 2.00 kg weight approximately weekly. Infants were weighted with minimum clothing e.g. wearing a vest only, on a calibrated Masskot electronic pan style scale as seen in Figure 5. The weight measurements were then plotted on the Road to Health Card in order to monitor the child's growth. Infants that faltered in growth were referred to the local health facility for further assistance.



Figure 5: Infant being weighed during a home visit in the Good Start Study

Recumbent length measurements were obtained using a roller meter (TALC). The infant was placed on the roller meter on his/her back with the crown of the head touching the fixed headboard and the shoulders touching the base of the roller meter. The field researcher then ensured that the infant's legs were straight and slid the movable foot board against the soles of the infant's feet. The recumbent length reading was then taken as shown in Figure 6.



Figure 6: Infant length measurement taken during a home visit in the Good Start Study

In order to: a) improve validity and, b) reduce inter and intra-observer bias, the anthropometry data collection was validated in accordance with the validation SOP. An initial validation exercise took place during the training of data collectors at local well baby clinics. The data collector supervisor (DCS) acted as the gold standard as they had the most experience in weighing and taking the length of infants. The DCS and a data collector would each weigh and measure an infant waiting for immunizations. They would each record the measurements without seeing each other's results. The mother would then take the baby to the nurse for immunizations. Following the session with the nurse the baby would again be weighed measured by both the DCS and the data collector. This process would continue until each data collector had weighed and measured 10-20 children twice. Disagreements in measurements were to be discussed and any identified problems addressed through further training. During the study, validation took the form of double measurements in the home where two data collectors went together on some visits and both

weighed and measured length of the infants. Antenatal and hospital records were also reviewed for antenatal, intra-partum, post-partum and PMTCT programme care information during all home visits (Good Start Study Group, 2002)

2.1.3.8 LAB METHODS: HIV TEST

Information on the maternal HIV status was obtained from the routine PMTCT medical records. Infants born to HIV-positive mothers were tested for HIV at 3, 24 and 36 weeks post-delivery. Their HIV status was determined from dried blood spots using a HIV-1 DNA polymerase chain reaction assay (Amplicor HIV-1 Monitor, version 1.5; Roche Molecular Systems, Branchburg, New Jersey, USA) (Jackson et al., 2007b).

2.1.3.9 METHODOLOGY FOR ASSESSING ANTHROPOMETRY

Anthropometric measurements are often reported as standard normal deviations (SD) or z-scores. The z-score or standard deviation unit is described as the difference between the value for an individual and the median value of the reference population for the same age or height, divided by the standard deviation of the reference population (World Health Organization, 1995).

Therefore:
$$z\text{-score} = \frac{(\text{observed value}) - (\text{median reference value})}{\text{Standard deviation of reference population}}$$

Equation 1: Z-score calculation

LAZ, WAZ and WLZ were calculated for each child using WHO Anthro-2005 software (Department of Nutrition, World Health Organisation, 20 Avenue Appia, 1211 Geneva 27, Switzerland). Cut-off points for z-scores are used to distinguish healthy infants from those that are malnourished. Cut-off points of minus three, two and one indicate severe, moderate and mild malnutrition respectively (Cogill, 2003). The minus two SD's is the most frequently used cut-off point and was used in this study (McMurray, 1996).

2.1.3.10 DATA ENTRY

Quantitative data were double-entered into a Microsoft Access (Microsoft 2003) database at a central site (Medical Research Council, Durban). The data was then validated and exported to Stata version 8 (Stata Corp., College Station, Texas, USA, 2003) for data management (Jackson et al., 2007b).

2.1.3.11 DATA MANAGEMENT

Data management, included the issuing of quality control reports, the tracking of study participants and documentation of every visit using a tracking log (participant specific codes were used for participant identification) and periodic site audits (McCoy et al., 2002).

2.1.4 ETHICS

2.1.4.1 ETHICS APPROVAL

The Good Start Study obtained ethical approval from the University of the Western Cape and the University of Kwa-Zulu Natal for the pilot and final study, respectively. The proposal for the thesis sub-study was approved by the University of Cape Town Ethics Committee (see appendix a and b respectively).

2.1.4.2 INFORMED CONSENT

Potential participants were given information about the study objectives, expected activities (home visits and blood tests), risks and benefits of participating in the study, before informed consent was requested. All sites used the same standard informed consent and information forms which were developed in English and translated into study languages namely; Xhosa, Zulu and Afrikaans. One consent form was signed for the interviews and another form was signed for HIV related testing of mother and infant. Signed informed consent was obtained from the participants at the time of enrolment into the study. Verbal consent was obtained at

each visit or data collection point thereafter, including prior to every blood draw or other specimen collection. Consent for the participation of the infant in the study was obtained from the mother. Participants were informed that they could withdraw from the study at any time with no repercussions on service provision (Jackson et al., 2007b).

2.2 THESIS SUB-STUDY (SECONDARY DATA ANALYSIS)

Data was exported into Stata version 10 (Stata Corp., College Station, Texas, USA, 2007) for analysis. A 5.00% significance level ($\alpha=0.05$) was used to guide statistical significance in the analyses.

2.2.1 SAMPLE SIZE

The work presented in this document is a secondary analysis of data collected during the primary study, the Good Start Study. The sample size calculations for the study were based on the main study objective, which was to measure the rate of vertical transmission of HIV-1 in mother-infant pairs in three settings namely Paarl, Rietvlei and Umlazi. It was estimated that recruitment over a period of 10 months would yield a total sample size of 700-800 HIV+ mothers. Assuming a transmission rate of 18% and a 30% lost to follow-up rate for a total of 490-560 HIV+ mother-infant pairs, this sample size would give a 95% confidence interval of +/- 3.5-4.0%. The sample size for each site was estimated to provide a precision in the HIV transmission (or death) rate at 9 months of +/-4.3% in Umlazi, +/-6.5% in Rietvlei and +/-7.5% in Paarl. The final Good Start cohort came to 883 mother-infant pairs. One third (218) of these mothers were HIV-negative while two thirds (665) were HIV-positive. Since this was secondary data analysis a sample size for this analysis was not undertaken prior to the start of the main study and a post hoc sample size calculation would therefore not be meaningful.

2.2.2 VARIABLES OF INTEREST

2.2.2.1 MALNUTRITION

Malnutrition, as measured by z-scores, was the outcome of interest in this analysis. An infant was considered moderately wasted, underweight or stunted when their WLZ, WAZ, or LAZ, respectively, fell below minus two SD. These z-scores were analysed both in the continuous and binary form.

Missing data and the presence of outliers in the dataset are the two data quality issues one needs to consider when working with anthropometric data, as they are both potential sources of bias (World Bank Institute, 2007).

Errors in the collection of data (infant body measurements and/or the reported age) can result in the calculation of biologically implausible z-scores (World Health Organization, 1995). Infants with these implausible z-scores were removed from the dataset in accordance with the World Health Organisation's (1995) exclusion criteria. Some infants did not have complete anthropometric data. Excluding all infants with incomplete outcome data from the analysis may bias the results. In order to avoid this, all available anthropometric data was included in the analysis. At each time point, all infants with anthropometric outcome data were included in the analysis. The failure to complete all scheduled visits is the main cause of the missing data. In general, data collectors were unable to collect anthropometric data because: 1) the infant died; 2) the infant was unavailable because the mother relocated from the study area and 3) the mother did not consent to the child's anthropometric measurements being taken (Good Start Study Group, 2002)

Data can either be: 1) missing, independent of both observed and unobserved data i.e. missing completely at random or 2) missing, dependent on observed data and not on unobserved data i.e. missing at random or 3) missing, dependent on unobserved data i.e. missing not at random (Little and Rubin, 1987). To test whether data was missing at random or not, the demographic data of infants with missing anthropometric data were compared against those of infants with complete data.

2.2.2.2 HIV

The main objective of this study was to assess the effect of HIV on infant growth. Infants were analysed according to their HIV exposure and infection status. Infants could either be; 1) HIV-positive infants born to HIV-positive mothers (infected), 2) HIV-negative infants born to HIV-positive mothers (uninfected) or 3) HIV-negative infants born to HIV-negative mothers (unexposed). Infants (n= 81) with an indeterminate HIV status were excluded from the analysis.

2.2.2.3 LOW BIRTH WEIGHT

Low birth weight (defined as an infant with a birth weight less than 2500g) was adjusted for in the multivariate analysis because of its association with poor infant growth. It was the only potential confounder adjusted for in the multivariate models. The adjusted models and unadjusted models gave comparable results. Only the adjusted models are presented in the results.

2.2.3 DESCRIPTIVE ANALYSIS

2.2.3.1 HISTOGRAMS

Histograms were used during the explanatory data analysis to illustrate the distribution of the data. The shape of the distribution informs one of the normality (or non-normality) of the data. Data is normally distributed when the mean, median and mode are similar. Graphically one would see a symmetrical (bell shaped) histogram indicating that the data is approximately normally distributed. The Shapiro-Wilk test, which detects departure from normality, was used to confirm the interpretation of the histograms. The shape of the distribution of the continuous variables informed the choice of method(s) used to analyse that variable.

2.2.3.2 BOX AND WHISKER PLOT

The box plot was used to graphically assess the distribution of data. It was also used to detect unusual observations (outliers) in the data.

2.2.4. UNIVARIATE ANALYSIS

2.2.4.1 MEDIAN TEST

The Median Test is a non-parametric test that tests the null hypothesis that several samples are drawn from populations with equal medians (Conover, 1971)

2.2.4.2 WILCOXON RANK SUM TEST

The Wilcoxon rank sum test assesses whether two independent samples have been drawn from the same population i.e. whether or not the distributions are similar (Siegel and Castellan, 1988).

2.2.4.3 F-TEST

The F-Test is used to assess whether or not two sample variances or standard deviations are similar (Box, 1953).

2.2.4.4 PEARSON CHI-SQUARE TEST

The Pearson's Chi-Square Test (χ^2 Test) was used to test whether paired observations on two variables, expressed in a 2X2 (or contingency table), were significantly independent of each other (Rao and Scott, 1981) .

2.2.4.5 ONE-WAY ANALYSIS OF VARIANCE (ANOVA)

ANOVA is a statistical technique used to compare the means of normally distributed observations of three or more groups (Gosset, 1908). Z-scores were explored in the continuous form and were summarised using means and confidence intervals. The mean z-scores of infected, uninfected and unexposed infants were compared at three visit times using ANOVA. The aim of this analysis was therefore to assess whether the anthropometric means of the three groups were at the same level at the three visit times. This analysis did not assess the effect of time on growth as infant growth was assessed cross-sectionally. Time was therefore kept constant.

2.2.4.6 TWO SAMPLE WILCOXON RANK SUM TEST

The Wilcoxon rank-sum (Mann-Whitney) test, is the nonparametric equivalent of the two sample t-test for independent samples (Wilcoxon, 1945)

2.2.4.7 BONFERRONI METHOD

ANOVA is a statistical method used to compare the means of three or more independent groups of observations. It was used to compare the means of the three infant groups in this study. ANOVA allows us to test whether the mean of at least one of the groups differs significantly from that of one other group. ANOVA is an overall test of significance. When the analysis of variance leads to a rejection of the null hypothesis, that is, when the overall comparison of groups is significant ($P < 0.05$), we need to determine which of the pairs should be rejected. A number of multiple comparison statistical methods are available on STATA e.g. the Scheffe Test, Sidak multiple comparison test, Bonferroni Method etc. The Bonferroni Method was used for multiple comparisons in this study in order to determine pair-wise differences. Performing a large number of pair-wise significance tests increases the probability of a type I error. In order to lower the risk of a type I error, the Bonferroni Method adjusts the statistical significance level (alpha) based on the number of comparisons being performed. It divides the overall probability (alpha) by the number of comparisons being made (Bland and Altman, 1995, Hair et al., 2006)

2.2.4.8 KRUSKAL WALLIS TEST

A nonparametric equivalent of the one-way ANOVA, the Kruskal Wallis Test, was used in the analysis when the assumptions of normality were not met (Kruskal and Wallis, 1952)

2.2.5 MULTIVARIATE REGRESSION ANALYSIS USING MIXED MODELS

The multivariate regression analysis aimed to answer the following three questions:

1. Were the anthropometric means of the groups the same? This tested for a group effect.
2. Were the anthropometric means flat? This tested for a time effect.
3. Were the anthropometric means parallel? This tested for a group* time interaction.

Anthropometric measurements were taken at three time points for each infant in the primary study. Longitudinal data analysis was therefore appropriate because we had a response profile for each infant. The anthropometric measurements, being taken from the same infant, were not independent of each other and were therefore correlated. Several methods are used to analyse data with repeated observations. One such method is the mixed effects (random coefficients) analysis which was used in this study and is presented in the format shown in Table 1 below.

Table 1: Dummy table of mixed effect model

<i>Dependent variable</i>	β <i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Group 1	X	X	X
Group 2	X	X	X
Time	X	X	X
Group 1* Time	X	X	X
Group 2* Time	X	X	X
Covariate	X	X	X
Constant	X	X	X

2.2.5.1 MIXED EFFECTS (RANDOM COEFFICIENTS) ANALYSIS

In mixed effect models the group effect is modelled as a random effect i.e. the regression coefficients in the model are allowed to vary between groups. Different groups have different intercepts as illustrated in the Figure 7 below (Twisk, 2003). Mixed effect models are performed using the xtreg function in STATA.

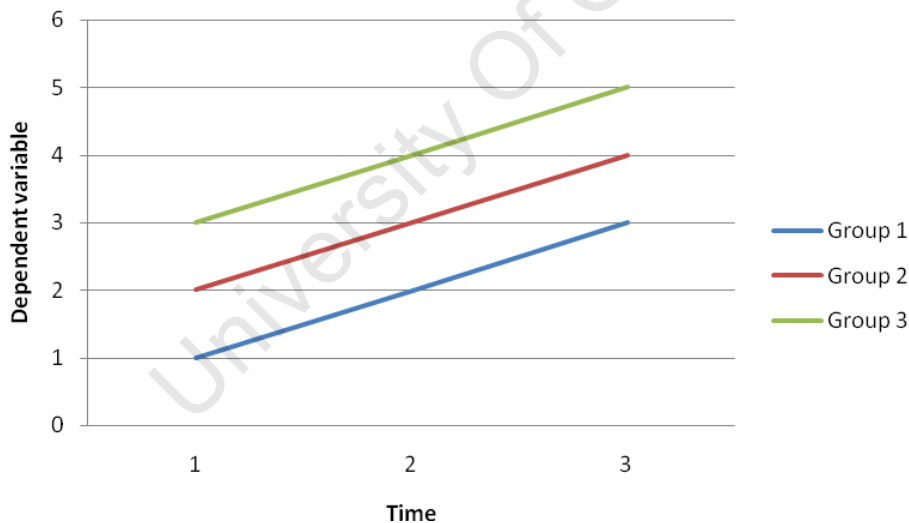


Figure 7: Different intercepts for different groups (Adapted from Twisk, 2003)

The development of the dependent variable over time is also allowed to vary amongst the groups in mixed effect models. This results in different gradients for the different groups as shown in Figure 8.

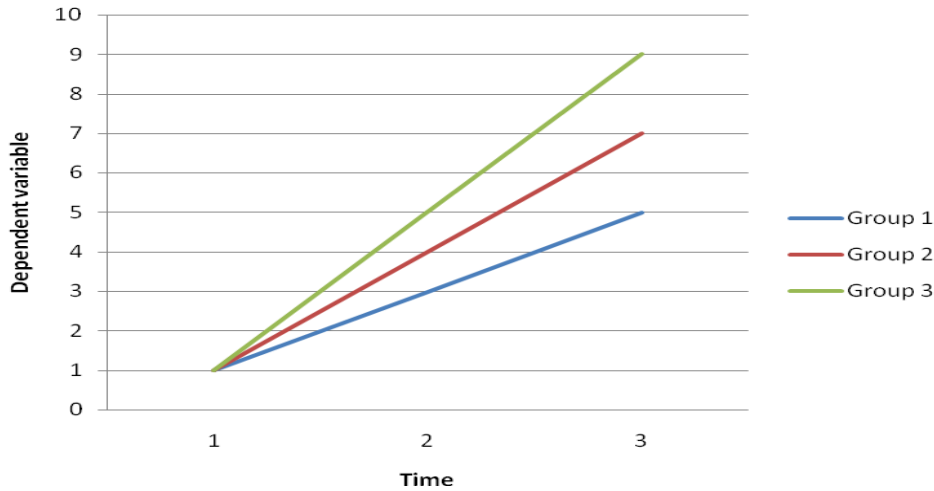


Figure 8: Different gradients for different groups (Adapted from Twisk, 2003)

The combination of the random intercept and random gradient with time gives rise to the equation below which is the longitudinal relationship between the continuous dependent variable and its independent variables (Twisk, 2003).

$$Y_{it} = \beta_{0i} + \sum_{j=1}^J \beta_{1ij} X_{ijt} + \beta_{2i} t + \sum_{k=1}^K \beta_{3ik} Z_{ikt} + \sum_{m=1}^M \beta_{4im} G_{im} + \varepsilon_{it} \quad \text{Equation 2}$$

Y_{it} are the observations for group i at time t , β_{0i} is the random intercept, β_{1ij} is the random regression coefficient for independent variable j , J is the number of independent variables, t is time, X_{ijt} is the independent variable j for group i at time t , β_{2i} is the random regression coefficient for time, β_{3ik} is the random regression coefficient for time-dependent k , K is the number of time-dependent covariates, Z_{ikt} is the time-dependent covariate k for group i at time t , β_{4im} is the random regression coefficient for time-independent covariate m , M is the number of time-independent covariates, G_{im} is the time-independent covariate m for group i , ε_{it} is the error for group i at time t . The β_{1ij} coefficients in the equation give the magnitude of the longitudinal relationship between the dependent variable and its independent variables. The equation also includes a time component because the dependent variable Y , and sometimes the independent variable X , is measured on the same group at several time points (Twisk, 2003).

The following features made mixed effect models appropriate for the current analysis:

- a) Mixed effect models assess the longitudinal relationship between a dependent variable and its independent variables using all available longitudinal data, i.e. without summarising measurements of each group into a single value such as the mean of the repeated measurements or a single measurement at the end of the follow-up period (Twisk, 2003). Since mixed effect models have a time component, they provide information on the history of the infants' growth. They differ from cross-sectional methods which only give data on the nutritional status of an infant at one point in time, without considering the effect of time on growth (McMurray, 1996).
- b) Mixed effect models adjust for the correlation between measurements taken from the same group by allowing regression coefficients to vary between groups (Twisk, 2003).
- c) Mixed effect models use the mle (maximum likelihood estimation) which enables them to cope better with missing data. This is however on condition that the data is missing at random. These models deal with missing data by assuming that the observed trend for a particular covariate pattern will continue during the unobserved period (Little and Rubin, 1987). Mixed effect models can handle datasets with missing data and this makes them appropriate for the current study as only 54.75% of the recruited participants had complete anthropometric data

2.2.5.1.1 MODELLING OF TIME

Visit time corresponds to the time when the anthropometric measurement was taken. It does not always correspond with the age of the infant because in some instances e.g. when the infant was ill or when the measuring instruments were malfunctioning, the anthropometric measurements were not taken. Data collection was postponed for the following week or fortnight. For calculation of age-based z-scores actual age

was used not visit time, while visit time was used to cluster z-scores within a time period e.g. 3 weeks, 24 weeks and 36 weeks.

Infant growth is a time-dependent variable so it does not always follow a linear trend in time. As a result, visit time could not be modelled as a continuous variable. Instead, visit time was modelled as a categorical variable with three categories namely 3, 24 and 36 weeks so that the real, non-linear, development of the dependent variable (infant growth) through time could be observed. Depending on the period being observed, the multivariate models either had the 3 or 24 week visit time as the reference time.

2.2.5.1.2 MODELLING OF THE GROUP EFFECT

Three groups of infants were considered: those infected by their HIV positive mothers (infected), HIV-negative infants born to HIV-positive mothers (uninfected), and HIV-negative infants born to HIV-negative mothers (unexposed). The unexposed infants were used as the reference group in all the models.

2.2.5.1.3 A GRAPHICAL REPRESENTATION OF INFANT GROWTH

Mean z-scores, stratified by infant HIV exposure and infection status, were plotted over time to assess infant growth. This method, which has also been applied by several other authors (Bailey et al., 1999, Bobat et al., 2001, Lepage et al., 1996, Masaka et al., 2007), was applied in this study so that the results could be comparable.

CHAPTER 3: RESULTS

3.1. RESPONSE RATE

One hundred and twenty eight (14.50%) of the 833 Good Start infants were excluded from this analysis in accordance with the WHO exclusion criteria for anthropometric outliers. The specific deletions are detailed in Table 2 below.

Table 2: WHO exclusion range for z-scores (World Health Organization, 1995)

Z-score	Range	Number of infants deleted
LAZ	< -5.0 and >+3.0	98
WLZ	< -4.0 and >+5.0	28
WAZ	< -5.0 and >+5.0	2
Total		128

A further 123 infants were excluded from the dataset because they had no available anthropometric data. Only 346 (54.75%) of the 632 remaining infants, had complete data for LAZ, WAZ and WLZ i.e. anthropometric data was collected at the 3, 24 and 36 week visit times. The rest of the sample consisted of infants with incomplete anthropometric data i.e. at least one missing measurement. This is shown in Table 3.

Table 3: Distribution of anthropometric data

Frequency	Percentage (%)	Cumulative %	Participants with outcome data		
			3 week visit time	24 week visit time	36 week visit time
346	54.75	54.75	✓	✓	✓
134	21.20	75.95		✓	✓
79	12.50	88.45	✓		
36	5.70	94.15	✓	✓	
22	3.48	97.63	✓		✓
9	1.42	99.05		✓	
6	0.95	100.00			✓
632	100.00				

We compared the demographic characteristics of those with missing data against those with complete data to identify systematic bias in the collection of data.

Table 4: Participant characteristics by anthropometric data availability

Explanatory variables	Missing	Not Missing	Median Test	F-Test	Wilcoxon Rank Sum Test
	Median(Range)	Median(Range)	P-value	P-value	P-value
Maternal age (Yr)	24 (13-42)	24(15-41)	0.27	0.37	0.30
Maternal education (Std)	8(1-10)	8(0-10)	0.08	0.33	0.05
Parity (No.)	2(0-7)	2(1-8)	0.44	<0.01	0.34
Birth weight (g)	3000(1000-4360)	3080(1600-4900)	0.26	0.52	0.31
Gestational age (Wks)	40(23-44)	40(31-42)	0.44	<0.01	<0.01

Infants with missing anthropometric data were not systematically different from those with complete data with respect to some maternal characteristics (median maternal age, maternal educational level and parity) and infant factors (birth weight), as seen in Table 4. The infants differed significantly, according to the Wilcoxon Rank Sum Test, with respect to parity and gestational age.

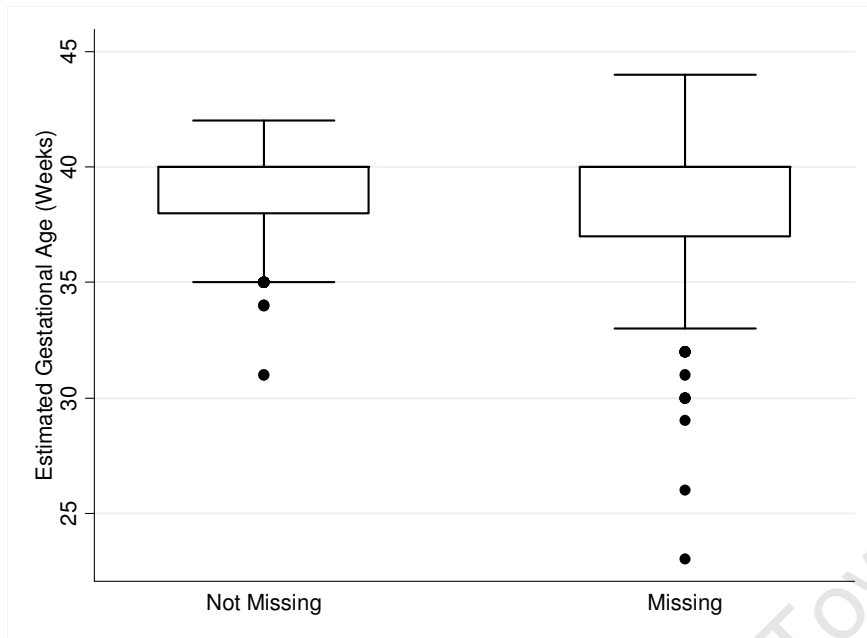


Figure 9: Box and Whisker plot of gestational age

The box and whisker plot in Figure 9 shows a difference in the distribution of the gestational ages of infants with complete anthropometric data and those with incomplete data.

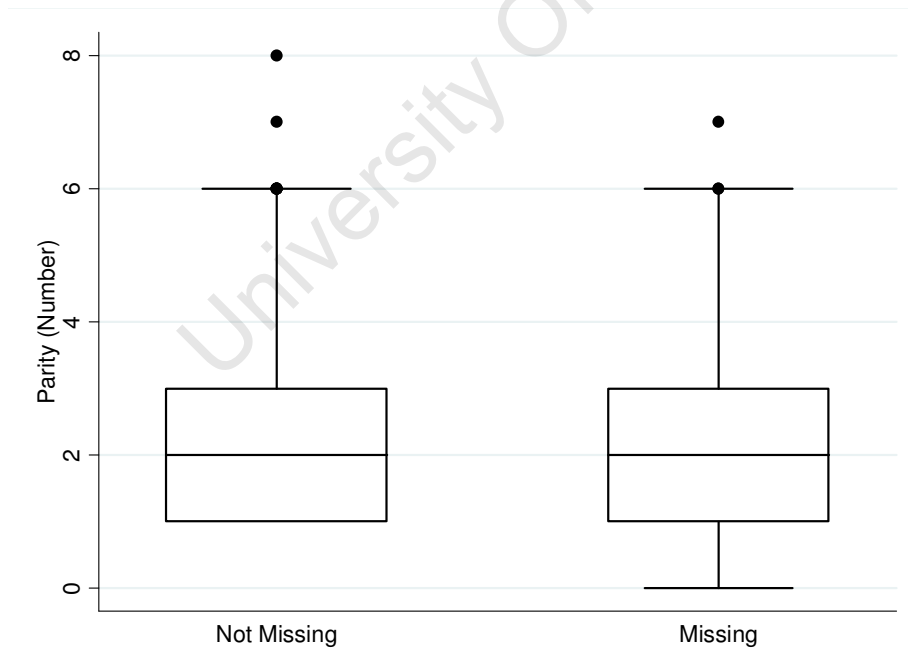


Figure 10: Box and Whisker plot of number of live births

The box and whisker plot in Figure 10 shows a difference in the distribution of the number of live infants born to mothers of infants with complete anthropometric data and those with incomplete data. The median number of live births (n=2) was the same.

3.2 DATA EXPLORATION

3.2.1 PARTICIPANT CHARACTERISTICS BY SITE

Table 5 gives details of some maternal factors, relevant for reporting on child growth outcomes, stratified by site.

Table 5: Participant characteristics by site

Characteristic	Paarl n= 190	Rietvlei n= 257	Umlazi n= 308	P-value ¹
Maternal				
Drinking water				
Piped	99.50%(n= 180)	43.00%(n= 96)	100.00%(n= 249)	<0.01
Non-piped	0.50%(n= 1)	57.00%(n= 127)	0.00%(n= 0)	
Source of fuel				
Electricity	46.00%(n= 81)	12.00%(n= 27)	66.00%(n= 159)	<0.01
No electricity	54.00%(n= 97)	88.00%(n= 189)	34.00%(n= 81)	
Toilet type				
Flush toilet	81.00%(n= 147)	2.00%(n= 4)	60.00%(n= 150)	<0.01
No flush toilet	19.00%(n= 35)	98.00%(n= 219)	40.00%(n= 99)	

1. P-value derived from Pearson chi Test

The majority (99.50%; n= 180) of the women living in Paarl (a peri-urban farming area) drank piped water. A large proportion (81.00%; n= 147) of these women had access to an indoor flush toilet. These women either used electricity (46.00%; n= 81), paraffin (36.00%; n= 63) or a gas stove (18.00%; n= 32) to prepare meals. Fifty seven percent (n= 127) of the women in Rietvlei (a rural area) drank non-piped water while 43.00% (n= 96) drank piped water. The majority (98.00%; n= 219) of these women did not have an indoor flush toilet. Wood was a source of cooking fuel for 68.00% (n= 147) of the women. Only 12.00% (n= 27) of the women used electricity. All the women sampled in Umlazi (a peri-urban township) drank piped water. Sixty percent (n= 150) of these women had access to an indoor flush toilet

while 40.00% (n= 99) used an outdoor toilet facility. Sixty six percent (n= 159) of the women used electricity to prepare meals.

The following is an analysis of anthropometric data from the 632 infants that were included in the final dataset. Histograms showed that the distributions for WAZ, WLZ and LAZ were normally distributed at the three visit times.

3.2.2 UNIVARIATE ANALYSIS OF Z-SCORES BY SITE

Tables 6-8 provide assessments of mean z-scores by site.

Table 6: Analysis of mean LAZ by site

LAZ						
Visit time (weeks)	Statistic	Paarl	Rietvlei	Umlazi	Total	*p-value
3	N (%)	173(37.61)	184(40.00)	103(22.39)	460(100.00)	<0.01
	Mean (95% CI)	-1.07 (-1.27;-0.88)	-1.04 (-1.24;-0.84)	-0.43 (-0.79; -0.07)		
24	N (%)	157(31.34)	161(32.14)	183(36.53)	501(100.00)	<0.01
	Mean (95% CI)	-0.21 (-0.43;0.01)	-0.75 (-0.95; -0.55)	-0.32 (-0.56; -0.09)		
36	N (%)	153(32.08)	148(31.03)	176(36.90)	477(100.00)	<0.01
	Mean (95% CI)	-0.16 (-0.38;0.06)	-0.73 (-0.93;-0.52)	0.59 (0.38;0.80)		

Note: *One-way ANOVA p-values

There were significant differences in mean LAZ among the sites at the three visit times, as shown in Table 6 above. Overall, infants in Umlazi had a relatively higher mean LAZ compared to infants in Paarl and Rietvlei. Analysis using the Bonferroni Test to assess the significance of this difference between the sites (data not shown) indicates that infants in Umlazi had a significantly ($P<0.05$) higher mean LAZ compared to infants in Rietvlei at the three visit times; and a significantly higher

mean LAZ compared to infants in Paarl at the 3 week (Bonferroni Test, $P<0.01$) and 36 week (Bonferroni Test, $P<0.01$) visit times. Infants in Rietvlei had the lowest mean LAZ compared to infants in the other two sites.

The one-way ANOVA results, in Table 7 below, show an overall significant difference in mean WAZ between the sites. A more detailed analysis, using the Bonferroni Test (data not shown), showed that infants in Rietvlei had a significantly lower mean WAZ compared to infants in Paarl at the 3 week ($P<0.01$) and 36 week ($P=0.02$) visit times; and a significantly lower mean WAZ compared to infants in Umlazi at the 24 week visit time ($P=0.05$).

Table 7: Analysis of mean WAZ by site

WAZ						
Visit time (weeks)	Statistic	Paarl	Rietvlei	Umlazi	Total	*p-value
3	N (%)	176(37.21)	185(39.11)	112(23.68)	473(100.00)	<0.01
	Mean (95% CI)	-0.37 (-0.55; -0.18)	-0.86 (-1.05; -0.67)	-0.68 (-0.93; -0.43)		
24	N (%)	158(30.39)	166(31.92)	196(37.69)	520(100.00)	0.03
	Mean (95% CI)	0.19 (-0.02; 0.40)	-0.13 (-0.31; 0.06)	0.19 (0.02; 0.35)		
36	N (%)	155(30.75)	158(31.35)	191(37.90)	504(100.00)	0.02
	Mean (95% CI)	0.44 (0.21; 0.66)	0.04 (-0.15; 0.23)	0.35 (0.17; 0.52)		

Note: *One-way ANOVA p-values

Mean WLZ differed significantly between the sites at the 3 and 36 week visit times. Infants in Rietvlei had a significantly (Bonferroni Test, $P<0.01$) lower mean WLZ compared to infants in Paarl at the 3 week visit time. Infants in Umlazi had the lowest mean WLZ at the 3 and 36 week visit time.

Table 8: Analysis of mean WLZ by site

WLZ						
Visit time (weeks)	Statistic	Paarl	Rietvlei	Umlazi	Total	*p-value
3	N (%)	174 (38.16)	186(40.79)	96(21.05)	456(100.00)	<0.01
	Mean (95% CI)	0.72 (0.54; 0.90)	-0.01 (-0.20;0.18)	-0.71 (-1.11; -0.30)		
24	N (%)	156(30.95)	164(32.54)	184(36.51)	504(100.00)	0.88
	Mean (95% CI)	0.58 (0.37; 0.78)	0.54 (0.35; 0.73)	0.62 (0.38;0.85)		
36	N (%)	152(31.87)	148(31.03)	177(37.11)	477(100.00)	<0.01
	Mean (95% CI)	0.81 (0.60; 1.02)	0.71 (0.51;0.90)	0.09 (-0.14;0.32)		

Note: *One-way ANOVA p-values

As seen in Table 8, WLZ differed significantly between the sites at the 3 week ($P<0.01$) and 36 week ($P<0.01$) visit times. Infants in Umlazi had lower mean WLZ compared to infants in Paarl and Rietvlei. No significant difference ($P=0.88$) in mean WLZ is evident between the sites at the 24 week visit time.

In summary, one can see from the results presented in tables 6-8 that mean WAZ and LAZ were lowest in Rietvlei infants. Infants in Umlazi had better WAZ and LAZ than the other sites, but worse WLZ.

3.2.3 PARTICIPANT CHARACTERISTICS BY GROUP

Participant characteristics, relevant for reporting on infant growth, are presented in the below. These characteristics were stratified by HIV exposure and infection status.

Table 9: Participant characteristics by group

Characteristic	Infected n= 98	Uninfected n= 386	Unexposed n= 193	P-value
Maternal				
Age (years) ¹	24(21-29)	24(21-29)	23(19-28)	0.01 ²
Parity ¹	2(1-3)	2(1-3)	1(1-2)	<0.01 ²
Education (standard) ¹	7.5(6-9)	8(6-9)	8(7-10)	0.04 ²
Drinking water				
Piped	79.00%(n= 77)	81.00%(n= 307)	79.00%(n= 136)	0.76 ³
Non-piped	21.00%(n= 21)	19.00%(n= 72)	21.00%(n= 36)	
Source of cooking fuel				
Electricity	57.00%(n= 55)	59.00%(n= 220)	56.00%(n= 92)	0.78 ³
No electricity	42.00%(n= 41)	41.00%(n= 151)	44.00%(n= 71)	
Toilet type				
Flush toilet	40.00%(n= 39)	48.00%(n= 184)	44.00%(n= 75)	0.26 ³
No flush toilet	60.00%(n= 59)	52.00%(n= 196)	56.00%(n= 96)	
Infant				
Gestational age (weeks) ¹	39(37-40)	40(38-40)	40(38-40)	0.12 ²
Birth weight (grams) ¹	3000 (2550-3200)	3100 (2800-3400)	3020 (2740-3400)	<0.01 ²
Gender				
Male	51.00% (n= 50)	46.00%(n= 177)	48.00%(n= 92)	0.65 ³
Female	49.00%(n= 48)	54.00%(n= 209)	52.00%(n= 101)	

1. Median (Inter-quartile range)

2. P-value derived from Kruskal Wallis Test

3. P-value derived from Pearson Chi Squared Test

There was an overall significant difference in maternal age between the groups (P=0.01).

There was a significant difference in median age between HIV-positive women with uninfected infants and HIV-negative women (Two-sample Wilcoxon rank-sum Test,

$P < 0.01$); between HIV-positive women with infected infants and HIV-negative women (Two-sample Wilcoxon rank-sum Test, $P = 0.03$). HIV-positive women, both those with infected and uninfected infants, were younger (median age=23) compared to HIV-negative women (median age=24). HIV-positive women with infected infants did not differ significantly in median age from those with uninfected infants (Two-sample Wilcoxon rank-sum Test, $P = 0.89$).

Parity also differed significantly ($P < 0.01$) between the groups.

There was a significant difference in the median parity between HIV-positive women with uninfected infants and HIV-negative women (Two-sample Wilcoxon rank-sum Test, $P < 0.01$). This significant (Two-sample Wilcoxon rank-sum Test, $P < 0.01$) difference in parity was also evident between HIV-positive women with infected infants and HIV-negative women. HIV-positive women, both those with infected and uninfected infants, had a greater number of live births ($n = 2$) compared to HIV-negative women ($n = 1$). There was no significant difference (Two-sample Wilcoxon rank-sum Test, $P = 0.58$) in median parity between HIV-positive women with infected infants and those with uninfected infants.

The groups differed significantly with respect to median maternal education ($P = 0.04$). There was a significant difference in median education between HIV-positive women with uninfected infants and HIV-negative women (Two-sample Wilcoxon rank-sum Test, $P = 0.03$); between HIV positive women with infected infants and HIV-negative women (Two-sample Wilcoxon rank-sum Test, $P = 0.03$). The median level of education attained by HIV-positive women and HIV-negative women was standard six and seven respectively. HIV-positive women with infected infants did not differ significantly in the median level of education they attained compared with uninfected infants (Two-sample Wilcoxon rank-sum Test, $P = 0.46$).

Median birth weight differed significantly ($P < 0.01$) between the groups.

There was a significant difference in median birth weight between infected infants and uninfected infants (Two-sample Wilcoxon rank-sum Test, $P < 0.01$). The median birth weight of infected infants was also significantly different from that of unexposed infants (Two-sample Wilcoxon rank-sum Test, $P < 0.01$). The median birth weight of infected infants (3000g) was significantly lower than that of uninfected infants

(3100g) and unexposed infants (3055g). No significant difference in birth weight was evident between unexposed infants and uninfected infants (Two-sample Wilcoxon rank-sum Test, $P=0.82$).

The groups did not differ significantly with respect to median gestational age ($P=0.42$). They also did not differ significantly with respect to the following maternal characteristics: type of toilet used (Pearson Chi Squared Test, $P=0.26$), source of drinking water (Pearson Chi Squared Test, $P=0.76$ -) and source of cooking fuel (Pearson Chi Squared Test, $P=0.78$).

3.3 UNIVARIATE AND MULTIVARIATE ANALYSIS OF Z-SCORES BY GROUP

3.3.1 WAZ BY INFECTION AND EXPOSURE STATUS

The main objective of this study was to compare the growth outcomes of three groups: HIV-positive infants born to HIV-positive mothers (infected), HIV-negative infants born to HIV-positive mothers (uninfected) and HIV-negative infants born to HIV-negative mothers (unexposed). Table 10 summarises the number of infants that were assessed for WAZ at the three visit times. It also shows the percentage of infants that were underweight in each group. It is followed by the univariate analysis of mean WAZ by group (Table 11) and the multivariate analysis which is adjusted for low birth weight (tables 12 and 13). This sub-section then concludes with a graphical representation of the analysis (see Figure 11). This data analysis approach was repeated for WLZ (see Tables 14-17) and LAZ (see Tables 18-21).

Table 10: Proportion of underweight (WAZ < -2) infants by group

Group	Infected		Uninfected		Unexposed	
	No.	%	No.	%	No.	%
3 weeks	18/68	26.47	33/280	11.79	16/121	13.22
24 weeks	9/63	14.29	7/313	2.23	8/141	4.64
36 weeks	9/51	17.65	9/310	2.90	4/139	2.90

As shown in Table 10, a greater percentage of infected infants (26.47%) were underweight compared to uninfected infants (11.79%) and unexposed infants (13.22%) at the 3 week visit time and at subsequent visit times. The frequency of childhood underweight was similar between uninfected infants and unexposed infants at the 3 and 36 week visit times. There was a greater proportion of underweight infants in the unexposed group compared to the uninfected group at the 24 week visit time.

The following univariate analysis assessed whether mean z-scores differed significantly between the infant groups.

3.3.1.1 UNIVARIATE ANALYSIS OF WAZ BY HIV INFECTION AND EXPOSURE STATUS

Table 11: Summary statistics of WAZ data by group

Visit time (weeks)	Statistic	Infected	Uninfected	Unexposed	Total	*p-value
3	N (%)	68(14.47)	281(59.79)	121(25.75)	470 (100.00)	<0.01
	Mean (95% CI)	-1.11 (-1.47;0.74)	-0.55 (-0.70;0.41)	-0.55 (-0.78;-0.32)		
24	N (%)	63(12.19)	313(60.54)	141(27.27)	517 (100.00)	<0.01
	Mean (95% CI)	-0.70 (-1.078;-0.32)	0.28 (0.15;0.40)	0.01 (-0.19; 0.21)		
36	N (%)	52(10.38)	310(61.88)	139(27.75)	501 (100.00)	<0.01
	Mean (95% CI)	-0.36 (-0.85;0.12)	0.42(0.28;0.55)	0.19 (-0.01;0.40)		

*One-way ANOVA

Infected infants had significantly (Bonferroni Test, $P < 0.01$) lower mean WAZ compared to uninfected infants at the 3 week visit time. The mean WAZ of infected infants was also significantly (Bonferroni Test, $P = 0.01$) lower than that of unexposed infants. There was no significant difference (Bonferroni Test, $P = 1.00$) in mean WAZ between uninfected infants and unexposed infants.

The mean WAZ of infected infants was significantly (Bonferroni Test, $P < 0.01$) lower than that of uninfected infants at the 24 week visit time. The mean WAZ of infected infants was also significantly (Bonferroni Test, $P < 0.01$) lower than that of unexposed infants. There was no significant difference (Bonferroni Test, $P = 0.08$) in mean WAZ between uninfected infants and unexposed infants.

Infected infants had a significantly lower mean WAZ compared to uninfected infants (Bonferroni Test, $P < 0.01$) and unexposed infants (Bonferroni Test, $P = 0.02$) at the 36 week visit time. There was no significant difference (Bonferroni Test, $P = 0.26$) in mean WAZ between uninfected infants and unexposed infants.

3.3.1.2 MULTIVARIATE ANALYSIS OF WAZ BY INFECTION AND EXPOSURE STATUS

Table 12: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and childhood underweight during the three week and 24 week visit times

<i>WAZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	-0.08	-0.32;0.16	0.54
Infected	-0.41	-0.75;-0.08	0.02
Visit time	0.02	0.01;0.04	<0.01
Uninfected* visit time	0.02	0.00;0.03	0.01
Infected* visit time	-0.01	-0.03;0.01	0.35
Low birth weight	-1.53	-1.77;-1.29	<0.01
Constant	-0.32	-0.53; -0.12	<0.01

Note: Mixed effect model using the unexposed group and the 3 week visit time as reference categories

Infected: The mean difference (-0.41) in WAZ between infected infants and unexposed infants was statistically significant ($P=0.02$) at the 3 week visit time.

24 week visit time: The difference in the mean WAZ between the 3 and 24 week visit time was statistically significant ($P<0.01$) for unexposed infants.

Uninfected* 24week visit time: The significant ($P=0.01$) interaction between the uninfected group and the 24 week visit time indicates that the mean difference in WAZ, between uninfected infants and unexposed infants, depends on the visit time. The beta-coefficient (0.02) represents the degree to which the mean difference in WAZ between uninfected and unexposed infants changes when the 3 week visit time is compared to 24 week visit time.

Low birth weight: Infants with low birth weight had significantly ($P<0.01$) lower WAZ compared to infants with normal birth weight at the 3 week visit time.

The beta coefficients for the uninfected group and the interaction term (infected group * 24 week visit time) were not statistically significant ($P>0.05$).

Table 13: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and childhood underweight during the 24 week and 36 week visit times

<i>WAZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	0.24	-0.01;0.48	0.05
Infected	-0.70	-1.05;-0.34	<0.01
Visit time	0.01	0.00;0.02	0.03
Uninfected* visit time	-0.00	-0.01;0.01	0.93
Infected* visit time	0.00	-0.02;0.02	0.77
Low birth weight	-1.02	-1.32;-0.73	<0.01
Constant	0.16	-0.04;0.36	0.12

Note: Mixed effect model using the unexposed group and the 24 week visit time as reference categories

Uninfected: The mean difference (0.24) in WAZ between uninfected infants and unexposed infants was statistically significant ($P=0.045$) at the 24 week visit time.

Infected: The mean difference (-0.70) in WAZ between infected infants and unexposed infants was statistically significant ($P<0.01$) at the 24 week visit time.

36 week visit time: The mean difference in WAZ between the 24 week and 36 week visit time was statistically significant ($P=0.02$) for unexposed infants.

Low birth weight: Infants with low birth weight had significantly lower WAZ compared to infants with normal birth weight ($P<0.01$) at the 24 week visit time.

The beta coefficients for the uninfected group and the interaction term (infected group * 36 week visit time) were not statistically significant ($P>0.05$).

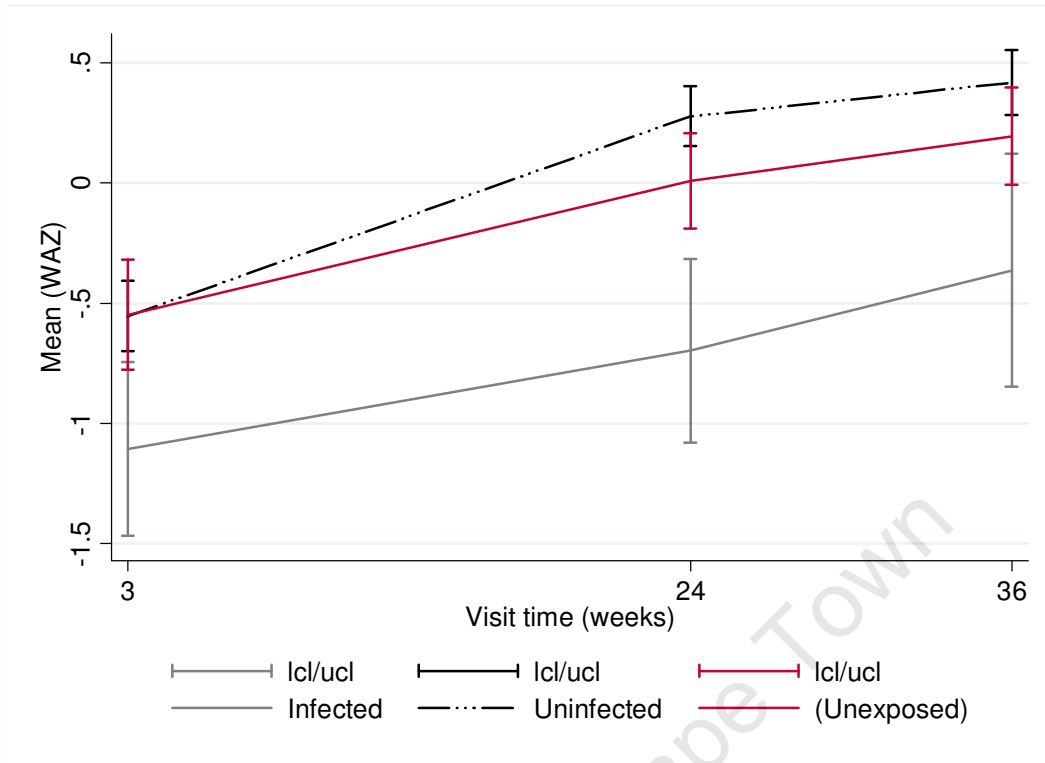


Figure 11: Childhood underweight mean z-scores versus visit time

Note: lcl is the lower confidence level; ucl is the upper confidence level

Table 11 shows a comparison of the mean WAZ of three groups of infants: the unexposed, infected and uninfected. This comparison is graphically illustrated in Figure 11. In summary, infected infants had a lower mean WAZ compared to uninfected infants and unexposed infants at the three visit times. The mean difference in WAZ was not significant between unexposed infants and uninfected infants at the three visit times. Results from the multivariate analysis showed a significant effect of time on the difference in mean WAZ between uninfected infants and unexposed infants. This group*-time interaction is illustrated by the gradients of the line plots in the figure above. As is evident in the figure, uninfected infants had a steeper gradient i.e. the growth trajectory which is the change in growth over time, compared to unexposed infants between the 3 and 24 week visit times. The growth trajectory of uninfected infants was not significantly different from that of unexposed infants between the 24 and 36 week visit times. This is illustrated by the parallel growth trajectories of these two groups between the 24 and 36 week visit times (see Figure 11).

3.3.2 WLZ BY HIV INFECTION AND EXPOSURE STATUS

Table 14: Proportion of wasted (WLZ < -2) infants by group

Group	Infected		Uninfected		Unexposed	
	No.	%	No.	%	No.	%
3 weeks	12/63	19.05	30/271	11.07	15/119	12.61
24 weeks	7/60	11.67	7/299	2.34	9/141	6.38
36 weeks	6/51	11.77	10/290	3.45	8/133	6.02

Table 14 shows the univariate analysis of mean WLZ by group. This is followed by the multivariate analysis in Tables 15 and 16, which is adjusted for low birth weight. Figure 12 is a graphical representation of mean WLZ stratified by group.

3.3.2.1 UNIVARIATE ANALYSIS OF WLZ BY HIV INFECTION AND EXPOSURE STATUS

Table 15: Summary statistics of WLZ data by group

Visit time (weeks)	Statistic	Infected	Uninfected	Unexposed	Total	*p-value
3	N (%)	63(13.91)	271(59.82)	119(26.27)	453 (100.00)	0.16
	Mean	-0.22	0.18	0.19		
	(95% CI)	(-0.66;0.22)	(-0.00;0.35)	(-0.10;0.47)		
24	N (%)	60(11.98)	300(59.88)	141(28.14)	501 (100.00)	<0.01
	Mean	0.02	0.72	0.52		
	(95% CI)	(-0.38;0.41)	(0.57;0.87)	(0.30;0.75)		
36	N (%)	51(10.76)	290(61.18)	133(28.060)	474 (100.00)	0.12
	Mean	0.23	0.59	0.43		
	(95% CI)	(-0.26;0.73)	(0.44;0.74)	0.18;0.69		

*One-way ANOVA

There was no significant difference in mean WLZ between the groups at the three week (P=0.16) and 36 week (P=0.20) visit times.

There was a significant difference ($P < 0.01$) in mean WLZ between the groups at the 24 week visit time. Infected infants had a significantly lower mean WLZ compared to uninfected infants (Bonferroni Test, $P < 0.01$) and unexposed infants (Bonferroni Test, $P = 0.05$). There was no significant difference in mean WLZ between uninfected infants and unexposed infants (Bonferroni Test, $P = 0.46$).

3.3.2.2 MULTIVARIATE ANALYSIS OF WLZ BY HIV AND EXPOSURE STATUS

Table 16: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and wasting during the three week and 24 week visit times

<i>WLZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	-0.03	-0.35;0.28	0.84
Infected	-0.29	-0.73;0.15	0.20
Visit time	0.02	0.00;0.03	0.05
Uninfected* visit time	0.01	-0.01;0.03	0.22
Infected* visit time	-0.01	-0.03;0.02	0.61
Low birth weight	-0.90	-1.20;-0.60	<0.01
Constant	0.28	0.02;0.55	0.04

Note: Mixed effect model using the unexposed group and the three week visit time as reference categories

Low birth weight: Infants with low birth weight had significantly lower WLZ compared to infants with normal birth weight ($P < 0.01$) at the three week visit time.

Table 17: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and wasting during the 24 week and 36 week visit times

<i>WLZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	0.21	-0.07;0.49	0.14
Infected	-0.40	-0.81;0.02	0.07
Visit time	-0.01	-0.03;0.00	0.19
Uninfected* visit time	-0.00	-0.03;0.02	0.81
Infected* visit time	0.01	-0.03;0.04	0.65
Low birth weight	-0.86	-1.18;-0.55	0.00
Constant	0.63	0.40;0.86	0.00

Note: Mixed effect model using the unexposed group and the 24 week visit time as reference categories

Low birth weight: Infants with low birth weight had significantly decreased WLZ compared to infants with normal birth weight ($P < 0.01$) at the 24 week visit time.

The beta coefficients for the group effects (both uninfected and infected groups) and those for the interaction terms (the uninfected* week visit time and the infected* week visit time) were not statistically significant ($P > 0.05$). This was evident between the three week and 24 week visit times and between the 24 week and 36 week visit times (as seen in Tables 16 and 17). The mean differences in WLZ between infected infants and unexposed infants and between uninfected infants and unexposed infants were therefore not statistically significant ($P > 0.05$).

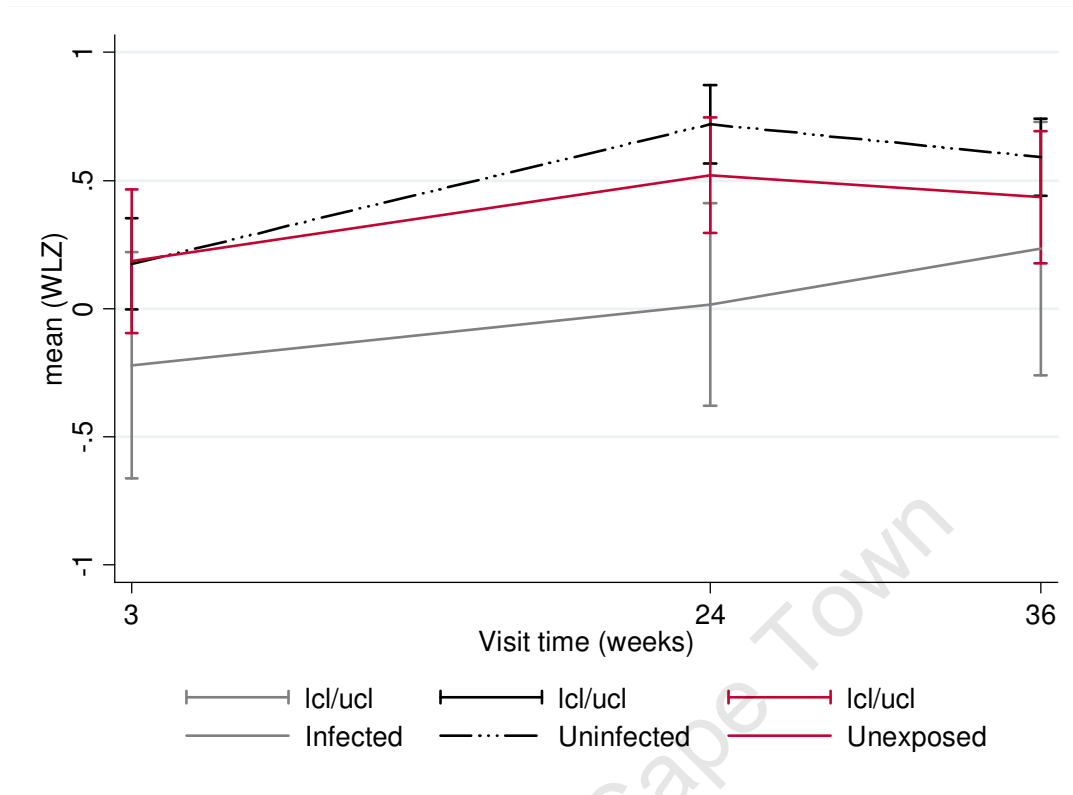


Figure 12: Wasting mean z-scores versus visit time

Note: lcl is the lower confidence level; ucl is the upper confidence level

A comparison of the mean WLZ between the three infant groups is shown in Table 15. This comparison is graphically illustrated in Figure 12 above. As shown in the figure, there were no significant differences in mean WLZ between the groups at the three week visit time. The Bonferroni Test shows a significant difference ($P=0.05$) in mean WLZ at the 24 week visit time between infected and unexposed infants. Infected infants had lower mean WLZ compared to unexposed infants. Both the univariate and multivariate analyses show no significant difference in mean WLZ between uninfected and unexposed infants at the 24 week visit time. There is no significant difference in mean WLZ between uninfected and unexposed infants and between infected and unexposed infants at the 36 week visit time. This result is also evident in Table 15 above.

The growth trajectories of the groups were not statistically different from each other and this is indicated by the insignificant interaction terms in Table 16 and Table 17.

3.3.3 LAZ BY HIV INFECTION AND EXPOSURE STATUS

As was previously done with the other two z-scores, mean LAZ were compared between the groups using one-way ANOVA. Mixed effect models were also performed to assess this comparison adjusted for low birth weight. Figure 13 is a graphical representation of the mean LAZ, at the three time points, stratified by group.

Table 18: Proportion of stunted (LAZ < -2) infants by group

Group	Infected		Uninfected		Unexposed	
	No.	%	No.	%	No.	%
3 weeks	17/63	26.98	59/272	21.69	20/122	16.39
24 weeks	18/60	30.00	34/299	11.37	19/139	13.67
36 weeks	15/51	29.41	16/292	5.48	19/131	14.50

3.3.3.1 UNIVARIATE ANALYSIS OF LAZ BY HIV INFECTION AND EXPOSURE STATUS

Table 19: Summary statistics of LAZ data by group

Visit time (weeks)	Statistic	Infected	Uninfected	Unexposed	Total	*p-value
3	N (%)	63(13.79)	272(59.52)	122(26.70)	457 (100.00)	0.50
	Mean (95% CI)	-1.12 (-1.53;-0.72)	-0.90 (-1.07;-0.72)	-0.86 (-1.11;-0.61)		
24	N (%)	60(12.05)	299(60.04)	139(27.91)	498 (100.00)	<0.01
	Mean (95% CI)	-1.09 (-1.49; 0.69)	-0.29 (-0.46;-0.13)	-0.44 (-0.68;0.20)		
36	N (%)	51(10.76)	292(61.60)	131(27.64)	474 (100.00)	<0.01
	Mean (95% CI)	-0.79 (-1.29;-0.30)	0.09 (-0.07;0.24)	-0.11 (-0.37;0.15)		

*One-way ANOVA

There was no overall significant difference ($P=0.50$) between the groups at the 3 week visit time.

There was a significant difference ($P<0.01$) in mean LAZ between the groups at the 24 week visit time. Infected infants had a significantly lower mean LAZ compared to uninfected infants (Bonferroni Test, $P<0.01$) and unexposed infants (Bonferroni Test, $P=0.01$). There was no significant difference in mean LAZ between uninfected infants and unexposed infants (Bonferroni Test, $P=0.96$).

There was a significant difference ($P<0.01$) in mean LAZ between the groups at the 36 week visit time. Infected infants had a significantly lower mean LAZ compared to uninfected infants (Bonferroni Test, $P<0.01$) and unexposed infants (Bonferroni Test, $P<0.01$). There was no significant difference in mean LAZ between uninfected infants and unexposed infants mean LAZ (Bonferroni Test, $P=0.56$).

3.3.3.2 MULTIVARIATE ANALYSIS OF LAZ BY HIV INFECTION AND EXPOSURE STATUS

Table 20: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and stunting during the three week and 24 week visit times

<i>LAZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	-0.11	-0.41;0.20	0.50
Infected	-0.23	-0.66;0.20	0.29
Visit time	0.02	0.00;0.03	0.01
Uninfected* visit time	0.01	-0.01;0.03	0.26
Infected* visit time	-0.02	-0.04;0.010	0.23
Low birth weight	-1.12	-1.40;-0.81	<0.01
Constant	-0.68	-0.94;-0.42	<0.01

Note: Mixed effect model using the unexposed group and the three week visit time as reference categories

24 week visit time: The difference in mean LAZ between the 3 and 24 week visit time is statistically significant ($P=0.01$) in unexposed infants.

Low birth weight: Infants with low birth weight had significantly lower LAZ compared to infants with normal birth weight ($P<0.01$) at the 3 week visit time.

The beta coefficients for the group effects (both uninfected and infected groups) and those for the interaction terms (the uninfected* 24 week visit time and the infected* 24 week visit time) were not statistically significant ($P>0.05$). The mean differences in LAZ between infected infants and unexposed infants and between uninfected infants and unexposed infants were therefore not statistically significant ($P>0.05$).

Table 21: Mixed effect model (adjusted for low birth weight) of longitudinal relationship between infant HIV status and stunting during the 24 week and 36 week visit times

<i>LAZ</i>	<i>Coefficient</i>	<i>95% CI</i>	<i>P value</i>
Uninfected	0.15	-0.14;0.44	0.32
Infected	-0.61	-1.05;-0.17	0.01
Visit time	0.03	0.01;0.05	<0.01
Uninfected* visit time	0.00	-0.02;0.03	0.75
Infected* visit time	-0.01	-0.04;0.03	0.69
Low birth weight	-0.65	-0.99;-0.32	<0.01
Constant	-0.36	-0.61;-0.12	<0.01

Note: Mixed effect model using the unexposed group and the 24 week visit time as reference categories

Infected: The mean difference (-0.61) in LAZ between infected infants and the unexposed infants was statistically significant ($P=0.01$) at the 24 week visit time.

36 week visit time: The mean LAZ of unexposed infants increased by 0.03 between the 24 and 36 week visit time and this increase was statistically significant ($P<0.01$).

Low birth weight: Infants with low birth weight had significantly lower LAZ compared to infants with normal birth weight ($P<0.01$) at the 24 week visit time.

The beta coefficients for the uninfected group effect and those for the interaction terms (the uninfected* 36 week visit time and the infected* 36 week visit time) were not statistically significant ($P>0.05$). The mean difference in LAZ between uninfected infants and unexposed infants was therefore not statistically significant ($P>0.05$).

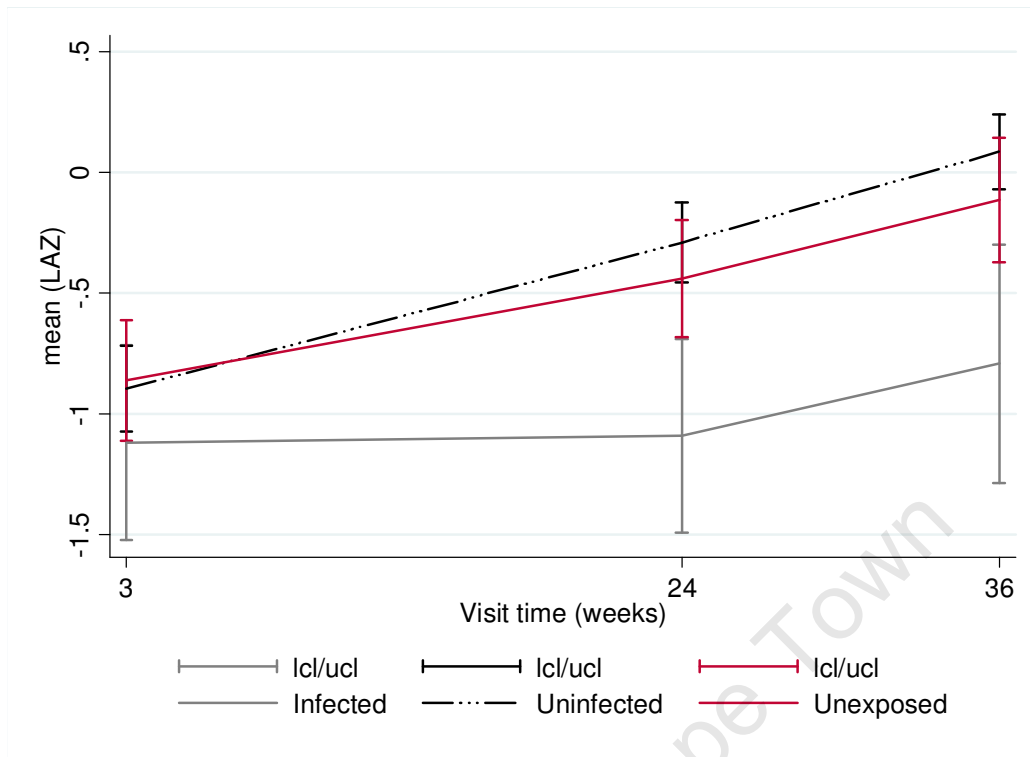


Figure 13: Stunting mean z-scores versus visit time

Note: lcl is the lower confidence level; ucl is the upper confidence level

The mean LAZ for unexposed, infected and uninfected infants are compared in Table 19. This comparison is graphically illustrated in Figure 13 above. At all the visit times, exposed infants and unexposed infants did not differ significantly in their mean LAZ. This result is evident in both the univariate and multivariate analysis. Infected infants had a significantly lower mean LAZ compared to unexposed infants at the 24 and 36 week visit times. Although mean differences in z-scores differed between some groups, growth trajectories did not differ significantly by group. This is indicated by the non-significant interaction terms in Table 20 and Table 21

CHAPTER 4: DISCUSSION

The following three sub-sections discuss the main findings in the context of other literature, using the study objectives as a framework.

4.1.1 MATERNAL AND INFANT CHARACTERISTICS

Infants with missing anthropometric data differed significantly from those with complete data with respect to parity and gestational age. Although the median parity was the same between the two groups, the standard deviation of the parity was not.

The median gestational ages of the two groups were the same. Although the medians (measure of central tendency) of the gestational ages of these two groups were the same, the distributions were not. The missing group had six outlying values for gestational age as compared to three outliers in the non-missing group. These values skew the distribution of the data towards one side. The more skewed nature of the missing data, together with the wider inter-quartile range of the missing data compared to the non-missing group, may partly explain why the distributions between the two groups were significantly different from each other.

These results indicate that infants with missing anthropometric data may have been systematically different from infants with complete anthropometric data with respect to parity and gestational age.

4.1.2 INFANT GROWTH AND HIV

The first objective of this study was to assess growth outcomes of HIV-exposed infants and unexposed infants. The analysis involved both univariate and multivariate statistical methods.

Results from the univariate analysis, which assessed the point prevalence of malnutrition, showed significant differences in mean z-scores between some of the groups. A comparison of the mean z-scores showed significantly lower mean WAZ in HIV-infected infants compared to uninfected infants at the three visit times. HIV-infected infants were therefore lighter compared to uninfected infants. This result is consistent with findings from other studies (Bailey et al., 1999, Bobat et al., 2001, Lepage et al., 1996, Patel et al., 2009). The loss of weight in people infected with HIV is reported to be associated with an increase in resting energy expenditure and protein turnover (Academy of Science of South Africa, 2007).

Mean LAZ was not significantly different between infected infants and unexposed infants at the 3 week visit time but was significant at the 24 and 36 week visit times. Bobat et al. (2001) and Patel et al. (2009) also reported no significant difference in mean LAZ between infected infants and unexposed infants at birth but a significant difference from 3 months onwards. The mean LAZ of infected infants was significantly lower than that of unexposed infants indicating that the infected infants were shorter in stature.

HIV-infected infants were significantly more wasted compared to uninfected infants at the 24 week visit time. No significant difference in mean WLZ was evident between HIV-infected infants and uninfected infants at the 3 and 36 week visit times. Similarly, the mean WLZ of infected infants was not consistently lower than that of uninfected infants in the Lepage et al. (1996) study. A significant difference in wasting was observed at ages 3, 6, 24 and 36 months. No significant difference was evident at ages 9, 12, 18, 21, 24, 27, 30, 33, 39 and 45 months (Lepage et al., 1996). It is suggested that HIV-infected infants could have experienced proportional declines in length and weight during these instances, resulting in them having WLZ similar to those of uninfected infants (Isanaka et al., 2009).

The univariate analysis revealed no significant difference in mean z-scores between uninfected infants and unexposed infants at the three visit times. The growth of uninfected infants was therefore comparable to that of unexposed infants at the three visit times, confirming results observed in other studies (Bailey et al., 1999, Lepage et al., 1996, Patel et al., 2009). This suggests that HIV infection, and not exposure, affects infant growth. The multivariate analysis, however, showed a striking difference in mean WAZ between uninfected infants and unexposed infants between the 3 and 24 week visit times. Uninfected infants had a steeper growth trajectory compared to unexposed infants. The greater rate of change in growth through time in uninfected infants compared to unexposed infants could be related to differences in infant feeding practices between HIV positive mothers and HIV negative mothers. Literature shows that mixed breast feeding (MBF), which involves feeding the infant breast milk together with other liquids and solids, was common among the HIV-negative Good Start Study mothers throughout the study period (Goga et al., [In Press]). Exclusive breastfeeding was uncommon amongst this group. Avoiding breast feeding was more (47.00%) common among the HIV-positive mothers compared to exclusive breast feeding (22.00%) at the 3 week visit time (Goga et al., [In Press]). Mothers who avoided breast feeding fed their infants commercial formula milk together with other nutritive and non-nutritive liquids and solids. This feeding practice is defined as mixed formula feeding (MFF) and was also observed at the 24 and 36 week visit times (Goga et al., [In Press]). This formula feeding of HIV uninfected infants could have resulted in the faster rate of growth of these infants compared to unexposed infants. Previously published studies have reported greater weight gain in formula fed infants compared to breastfed infants (Dewey et al., 1992, Dewey et al., 1993, Dewey, 1998a, Dewey, 1998b). This is mainly attributed to the higher intakes of both energy and protein by formula fed infants compared to breastfed infants (Heinig et al., 1993).

4.1.3 FREQUENCY OF MALNUTRITION

The second objective was to report on the frequency of stunting, wasting and childhood underweight in the three groups. Stunting, wasting and childhood

underweight were more pronounced in HIV-infected infants. These infants remained more malnourished compared to uninfected infants and unexposed infants throughout the study period. Research has found that HIV-infected infants do not catch-up in growth outside of interventions such as ARV treatment (Academy of Science of South Africa, 2007). None of the infants in this study were on ARV treatment as the study was conducted before paediatric ARV treatment became available.

4.1.4 INFANT GROWTH AND SITE

The third objective of this study was to compare the anthropometric outcomes of infants living in Paarl, Rietvlei and Umlazi. Results showed that stunting was most common amongst infants from Rietvlei, which was the least developed of the Good Start sites. Households in this area generally drank non-piped water, did not have an indoor flush toilet and used wood as a source of cooking fuel. A study by (Jones et al., 2008) showed that access to an indoor flush toilet was a predictor of stunting in a cohort of 1 year old Filipino infants. This could be due to the fact that infants living in environments with poor sanitation, such as those with no indoor flush toilet, are likely to get infections which have been shown to have a synergistic relationship with stunting (Jones et al., 2008).

Stunting was least prevalent in Umlazi, a peri-urban township area in Kwa-Zulu Natal. All the participants sampled in Umlazi drank piped water. The majority of these participants had access to an indoor flush toilet and used electricity to prepare meals. Infants in Umlazi were significantly longer (greater LAZ) than those in Paarl and Rietvlei. Their weight (WAZ) was between that of infants in Paarl and Rietvlei. When their LAZ and WAZ were combined into the WLZ measurements, these infants had the lowest WLZ. As is widely known, length measurements are less reliable compared to weight measurements. While it was not examined specifically, no indication was seen over the course of the study to indicate that length was less reliably measured in Umlazi compared to the other two sites. Therefore poor measurement of infants in Umlazi is not a likely explanation for the above-mentioned results. Another possible explanation could be missing data. Infants in Umlazi had

significantly (Pearson chi, $P < 0.01$) more missing anthropometric data ($n=78$) compared to infants in Paarl ($n=9$) and Rietvlei ($n=36$).

Infants in Paarl, a peri-urban farming area, were more stunted compared to infants in Umlazi. These results are consistent with data from the latest National Food Consumption Survey which showed that stunting is more prevalent in rural formal areas (commercial farms) compared to urban formal areas (Labadarios, 2008). This partly explains why stunting was more prevalent in Paarl, which is partially comprised of a farming population, compared to Umlazi. (Jackson et al., 2007a) propose that stunting in Paarl children could be associated with the high (>20.00% compared to a national prevalence of 15.00%) rate of low birth weight in that region. This low birth weight rate is largely attributable to intrauterine growth restriction from high smoking and alcohol use in pregnancy, which puts infants at risk of being stunted in childhood.

4. 2 STRENGTHS OF THIS STUDY

The repeated measures taken in longitudinal studies require data analysis methods that adjust for the correlation that exists between these repeated measures (Isanaka et al., 2009). The mixed effects (random coefficients) analysis was used in this study to account for this correlation. The use of mixed effect modelling to assess the relationship between HIV infection and/or exposure and infant growth makes this study particularly unique from previously published research (Bailey et al., 1999, Bakaki et al., 2001, Bobat et al., 2001, Lepage et al., 1996). The modelling allowed for a comparison of growth cross-sectionally at the three time points and longitudinally by comparing the growth trajectories. The longitudinal data analysis not only allowed the comparison of point prevalence of malnutrition at the three visit times, but also enabled an assessment of the rates of growth between the groups.

- To my knowledge, this study is one of the first to compare the growth of three groups of South African infants: 1) HIV-infected infants; 2) uninfected infants that were exposed to HIV and 3) unexposed infants born to HIV-negative mothers. Patel et al. (2009) also compared growth patterns amongst three groups of infants in South Africa. Their comparison was however restricted to differences in weight gain. They did not assess differences in linear growth between the infant groups. This work is also different from the analysis done by Bobat et al. (2001). Their work was restricted to infants born to a cohort of HIV-positive South African women. A comparison group of infants born to HIV-negative mothers was not included in the study.
- The growth patterns of the infected infants were compared against those of uninfected infants in the univariate analysis of this study. Seeing that these infants were all born of HIV-infected mothers, this comparison assessed infant growth while controlling for socio-economic differences that may have existed between infants of HIV-positive mothers and those of HIV-negative mothers. Including a group of unexposed infants in the current study enabled comparison of growth of HIV exposed infants against that of a population-based control group of unexposed infants. Therefore infant growth was also explored by HIV exposure status.

4.3 STUDY LIMITATIONS

- This study involved a secondary analysis of data collected during the Good Start Study. One disadvantage of doing secondary analysis is that one uses data that were collected for another purpose. The sampling frame, research questions, and data collection process were designed to address the objective of the primary study (Coyer and Gallo, 2005). Unlike in the primary study, the main objective of this secondary analysis was to assess malnutrition in three infant cohorts at three time points. A change in the study objective affects the extent to which the existing data can be used to address new questions. The current analysis was limited to drawing conclusions about associations and was not used to assess causality. Another disadvantage of secondary data

analysis is that the researcher has no influence over the data collection process (Coyer and Gallo, 2005). The secondary analysis is therefore often limited by data availability and quality. Anthropometric data quality was addressed according to the WHO guidelines in this study and this is detailed in sub-section 2.2.2.1 below. Secondary analysis was performed on all available information subsequent to data cleaning. A sample size estimation for this analysis would therefore be hypothetical and would not be a true reflection of the rigour of the analysis. Nevertheless secondary analyses are considered a valid design when source data used in the analyses are seen to have been validly collected as was the case in the Good Start Study.

Not all of the anthropometric data were available for analysis. As mentioned before, a total of 883 infants were recruited in the Good Start study. One hundred and twenty eight (14.50%) of the 833 Good Start infants were excluded from this analysis in accordance with the WHO exclusion criteria for anthropometric outliers. A further 123 infants were excluded from the dataset because they had missing anthropometric data. The remaining 632 (71.57%) infants had anthropometric data for some of the visit times i.e. at least one missing measurement. This attrition, referred to as intermittent missing data, was for the most part at random in this sample (Twisk, 2003). Only 346 (54.75%) of these 632 infants had complete anthropometric data. This data quality issue is not unique to this study as it is a known limitation of longitudinal studies. Patel et al. (2010) also reported similar data quality issues. They assessed child growth by maternal and child HIV status in a cohort of South African children. A total of 1498 children were born to HIV-infected mothers. Thirty-six pairs of twins and 43 children with reported extreme gestational ages were excluded from the total. A further 122 children were excluded from the dataset leaving 1261 children (84.18%), with at least one weight measurement after birth, for analysis. A total of 1432 children were born to HIV-uninfected mothers. Of these, 1061 (74.09%) were considered in the analysis. Hence the current study is consistent with losses seen in similar anthropometry studies and could be considered valid in the context of current literature.

- The current study assessed associations between HIV (infection or exposure) and infant growth and did not explore causal relationships. Seeing that both infant growth and HIV status are time varying variables, results from this study may be subject to temporality. One cannot establish from results in this study whether poor growth predisposed the infant to HIV infection or whether HIV infection leads to poor growth. However, given that the infants were infected by three weeks of age it is unlikely that the poor growth predisposed the infants to infection and many of the relationships between infection status and growth remained significant after adjusting for low birth weight.
- Another limitation is that some infants, that were HIV negative at the 3 week visit time, could have sero-converted during the follow-up period. Nevertheless, early transmission has consistently been seen in the literature to be the strongest predictor of child morbidity and mortality (UNAIDS, 2010) so we have also concentrated on this factor in this analysis.
- As is common in observational cohort studies, this study is subject to bias. Bias could have been introduced through self-selection of participants into the infant feeding groups. In randomized controlled trials this problem is resolved by blind-selecting the participants and assigning them into an exposure group. Randomization is used to control for both known and unknown confounders. To control for the potential confounding effect of birth weight, we adjusted for this variable in the mixed effect models. We however did not adjust for other confounders that are associated with infant growth e.g. gestational age. Low Birth Weight and gestational age are highly correlated so including both in the models may have led to collinearity issues and it was felt that low birth weight was the more direct measure being an anthropometric indicator.
- Single anthropometric measurements were taken by individual data collectors. These measurements are therefore subject to measurement error and intra-observer bias, even though validity checks were performed periodically to improve the validity of the data. The validity of the measurements, especially the less reliable length measurements, could have been improved by

averaging the length or weight measurements of two independent data collectors. Dual measurement however was not practical in this setting and validity checks during the study suggest current data is reasonably valid and reliable.

- The infants with complete anthropometric data differed significantly from those with missing anthropometric data with respect to parity and gestational age. The median gestational age was similar between the two groups but the distribution of the gestational ages differed significantly. The difference in the distributions can be attributed to the influence of extreme gestational age values, depicted in the box and whisker plots, on the spread of the data. Gestational age was approximated using information on the date of the last menstrual period and by abdominal palpation, methods of estimation are subject to measurement error. This may have resulted in the extreme gestational age values being calculated. Infants with extreme gestational ages were not excluded from the analysis. Gestational age was not adjusted for in the analysis and the rationale for this is noted above.
- Another limitation is the poor adherence to exclusive infant feeding amongst both HIV-positive and HIV-negative women in the Good Start sample. The homogeneity of feeding practices, due to the majority of the mothers mixed feeding, limited the extent to which differences in growth could be assessed across different infant feeding practices.

4.4 GENERALISABILITY OF RESULTS

The generalisability of the study findings is limited to other South African settings with similar characteristics (social, demographic, economic and HIV prevalence) as Paarl, Rietvlei and Umlazi.

4.5 RECOMMENDATIONS

4.5.1 EARLY IDENTIFICATION OF HIV-INFECTED INFANTS

- The results from this study show that HIV-infected infants have poorer growth outcomes compared to uninfected infants. This therefore emphasizes the importance of early infant HIV diagnosis to identify these high risk infants and rapid commencement of appropriate care and treatment. Early and continued infant growth monitoring, particularly in HIV exposed infants is also critical as growth retardation can be used as a marker of vertical transmission in the absence of DNA PCR confirmation.

4.5.2 EARLY INITIATION OF ARV THERAPY & TREATMENT OF OPPORTUNISTIC INFECTIONS

- HIV-infected infants in this study remained more malnourished compared to uninfected infants. Early identification of HIV positive infants at or before 6 weeks is therefore important as it will facilitate the timely placement of eligible infants on ARV therapy, which has been shown to have a positive effect on growth(Violari et al., 2008). The new national PMTCT protocol to be implemented from April 1st 2010 (The Presidency, 2009) recommends that all infants diagnosed HIV positive before one year of age should be started on ARV treatment immediately. This should have a notable impact on the growth of these infants.
- In addition, an improvement in the prevention and treatment of opportunistic infections through provision of Cotrimoxazole prophylaxis in HIV-positive infants can contribute to the reduction of malnutrition considering that illness affects both the intake and absorption of nutrients (Academy of Science of South Africa, 2007). Data from the Good Start study has shown that coverage of Cotrimoxazole was low in both Umlazi and Rietvlei sites(Jackson et al., 2007b)

4.5.3 STRENGTHNING OF NDoH PROGRAMMES

Malnutrition has a synergistic relationship with infections. An infant infected with HIV, which is a chronic infection, has a high chance of not catching up in growth and of dying. Research shows that HIV-infected infants who are not on ARV treatment do not catch-up in growth even if food intake is adequate. Malnutrition was more common among HIV-infected infants in this study. The majority of the paediatric HIV infections in South Africa are either acquired perinatally, during labour, or postnatally due to poor feeding practices (Academy of Science of South Africa, 2007). Therefore, prevention of HIV infection needs to be intercepted at these three points. The role out of ARV prophylaxis through PMTCT in South Africa has made it possible for many infants, born to HIV-positive mothers, to remain HIV-negative. The new PMTCT regimen with HAART for women with CD4 counts below 350 and dual prophylaxis for those with CD4 counts above 350 needs to be scaled up as this should dramatically reduce HIV infection and therefore malnutrition in infants and children.

An analysis of the frequency of malnutrition showed that malnutrition was still prevalent amongst uninfected infants at the time of the study. Malnutrition is therefore still a reality in the absence of the HIV epidemic. More effort needs to be fuelled into reducing the prevalence of malnutrition in the general child population in South Africa. The prevalence of malnutrition can also be reduced through the strengthening of other programmes adopted by the NDoH. These include the Integrated Nutrition Programme (INP), Expanded Program on Immunization (EPI), Integrated Management of Childhood Illnesses (IMCI) and the WHO 10 STEPS for management of severe malnutrition.

4.5.4 PROMOTE EXCLUSIVE INFANT FEEDING

- Universal coverage with exclusive breastfeeding (EBF) and continued breastfeeding (BF) – i.e. breast milk and complementary foods - up to one year may prevent 13.00% of under-five deaths globally, even in the presence of HIV. Exclusive infant feeding rates were low in the Good Start sample.

Mixed feeding, which increases the risk of vertical transmission, was the predominant infant feeding practice. There is therefore an urgent need to improve the promotion of exclusive infant feeding practices.

4.5.5 IMPROVE SURVEILLANCE OF INFANT GROWTH OUTCOMES

- Surveillance of malnutrition rates at the national level needs to be more frequent. Current malnutrition rates are based on the South African Demographic and Health Survey (DHS) from 1998. National wasting and stunting statistics for the 6-71 months age bracket are derived from the 1999 SAVACG Survey. National statistics for childhood under weight, stunting and wasting for both the 12-71 month and 1-9 years age brackets are taken from the 1998 DHS. An increase in childhood malnutrition can be used as an indicator of underlying events such as the increase in diarrheal diseases in infants or the malfunctioning of PMTCT programmes resulting in an increase in MTCT and a subsequent increase in malnutrition. An improvement in the monitoring of malnutrition can therefore enable the government and other interest groups to identify and to respond to such events more effectively.
- There is also a need for national malnutrition statistics for infants younger than 6 months so that the impact of programmes such as the INP and PMTCT can be monitored. In resource poor settings with poor sanitary conditions and lack of clean water, formula fed infants are at a greater risk of diarrheal diseases which may lead to malnutrition. Breastfeeding is a more preferable feeding option in such environments. The impact of interventions such as exclusive breastfeeding on the prevalence of malnutrition can only be seen if malnutrition indicators are also collected for infants less than 6 months.

4.6 FUTURE RESEARCH

- The current study assessed associations between HIV (infection or exposure) and infant growth and did not explore causal relationships. Further exploration of the direction and magnitude of the association between these variables is needed.

- The comparison of infants by feeding mode was limited by the high levels of mixed feeding in the cohort. Mixed feeding is associated with an increased risk of MTCT which ultimately puts the infant at risk of malnutrition. Therefore studies assessing the relationship between growth and exclusive infant feeding practices amongst HIV-infected and uninfected infants are needed.

University Of Cape Town

REFERENCES

- ACADEMY OF SCIENCE OF SOUTH AFRICA 2007. HIV/AIDS, TB and nutrition: Scientific inquiry into the nutritional influences on human immunity with special reference to HIV infection and active TB in South Africa. Pretoria: Academy of Science of South Africa
- BAILEY, R. C., KAMENGA, M. C., NSUAMI, M. J., NIEBURG, P. & ST LOUIS, M. E. 1999. Growth of children according to maternal and child HIV, immunological and disease characteristics: a prospective cohort study in Kinshasa, Democratic Republic of Congo. *International Journal Epidemiology*, 28, 532-540.
- BAKAKI, P., KAYITA, J., MOURA, M., JORGE, E., COULTER, J. B. S., TINDYEBWA, D., NDUGWA, C. M. & HART, C. A. 2001. Epidemiologic and clinical features of HIV-infected and HIV-uninfected Ugandan children younger than 18 months. *Journal of Acquired Immunodeficiency Syndrome*, 28, 35-42.
- BARRON, P., DAY, C., LOVEDAY, M. & MONTICELLE, F. 2005. The district health barometer year 1: January-December 2004. Durban: Health Systems Trust.
- BEISEL, W. R. 1996. Nutrition and immune function: overview. *The journal of nutrition*, 126, 2116S-2615S.
- BETTYLOU, S., EMBREE, J. E., MEI, Z., NDIYA-ACHOLA, J., NJENGA, S., MUCHUNGA, E. R., BETT, J. & PLUMMER, F. A. 2000. Sociodemographic characteristics, care, feeding practices and growth of cohorts of children born to HIV-1 seropositive and seronegative mothers in Nairobi, Kenya. *Tropical Medicine and International Health*, 5, 678-686.
- BLACK, R. E., ALLEN, H. L., BHUTTA, A. Z., CAULFIELD, E. L., DE ONIS, M., EZZATI, M., MATHERS, C. & RIVERA, J. 2008. Maternal and child undernutrition: global and regional exposures and health consequences. *The Lancet*, 371, 243-260.
- BLAND, J. & ALTMAN, D. 1995. Multiple significance tests: the Bonferroni method. *British Medical Journal*, 310, 170.
- BOBAT, R., COOVADIA, H., MOODLEY, D., COUTSOUDIS, A. & GOUWS, E. 2001. Growth in early childhood in a cohort of children born to HIV-1 infected women from Durban, South Africa. *Annals of Tropical Paediatrics*, 21, 203-210.
- BOX, G. E. P. 1953. Non-normality and tests on variances. *Biometrika*, 40, 318-335.
- BRADSHAW, D., BOURNE, D. & NANNAN, N. 2003. What are the leading causes of death among South African children? . Cape Town: Medical Research Council.
- CHOPRA, M. & DARNTON-HILL, I. 2006. Responding to the crisis in sub-Saharan Africa: The role of nutrition. *Public Health Nutrition*, 9, 544-550.
- CHOPRA, M., DAVIAUD, E., PATTISON, R., FONN, S. & LAWN, J. E. 2009. Saving the lives of South Africa's mothers, babies, and children: can the health system deliver? *Lancet*, 374, 835-46.
- COGILL, B. 2003. Anthropometric indicators measurement guide. *Food and nutritional technical assistance project*. Washington D.C.: Academy for Educational Development.
- CONOVER, W. J. 1971. *Practical nonparametric statistics*, New York, London, Sydney, Toronto, John Wiley and Sons Inc.
- DAY, C. & GRAY, A. 2007. *Health and related indicators. In: South African Health Review 2007*, Durban, Health Systems Trust.
- DE ONIS, M., BLÖSSNER, M., BORGHI, E., FRONGILLO, E. A. & MORRIS, R. 2004. Estimates of global prevalence of childhood underweight in 1990 and 2015. *JAMA*, 291, 2600-2606.

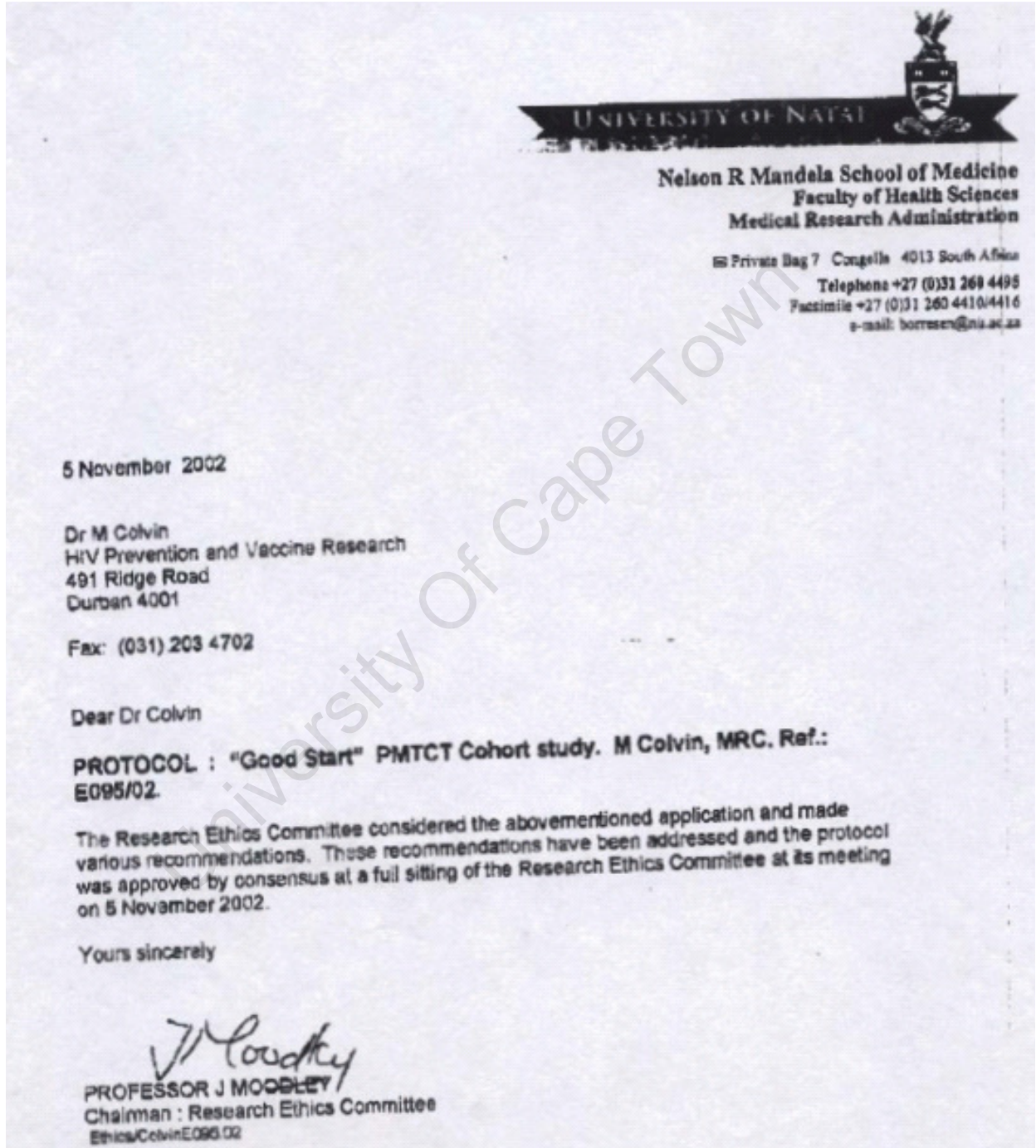
- FABER, M. & WENHOLD, F. 2007. Nutrition in contemporary South Africa. *Water SA*, 33, 393-399.
- FAMILY HEALTH INTERNATIONAL. 2007. HIV, Nutrition, and Food: A practical guide for technical staff and clinicians. North Carolina: Family Health International.
- GOGA, A. E., COLVIN, M., DOHERTY, T., JACKSON, D. J., SANDERS, D., CHOPRA, M. & KUHN, L. [In Press]. Poor feeding practices at routine PMTCT sites, but more exclusive feeding amongst HIV-positive women compared with negative women. *Journal of Nutrition*.
- GOOD START STUDY GROUP 2002. Good Start Study: National PMTCT Cohort Study Protocol. Health Systems Trust, University of the Western Cape, Medical Research Council, University of KwaZulu-Natal, National Department of Health, CADRE.
- GOSSET, W. S. 1908. The probable error of a mean student. *Biometrika*, 6, 1-25.
- GOVERNMENT OF SOUTH AFRICA & UNITED NATIONS 2005. South Africa: millennium development goals country report. Pretoria: National Department of Health.
- HAIR, J. F., BLACK, B., BABIN, B., ANDERSON, R. E. & TATHAM, R. L. 2006. *Multivariate Data Analysis (6th Edition)* Prentice Hall
- HEINIG, M. J., NOMMSEN, L. A., PEERSON, J. M., LONNERDAL, B. & DEWEY, K. G. 1993. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: the DARLING Study. *The American Journal of Clinical Nutrition*, 58, 152-161.
- ISANAKA, S., DUGGAN, C. & FAWZI, W. W. 2009. Patterns of postnatal growth in HIV-infected and HIV-exposed children. *Nutrition Review*, 67, 343-359.
- JACKSON, D., BATISTE, E. & RENDALL-MKOSI, K. 2007a. Additive effect of smoking and alcohol use during pregnancy on the occurrence of low birthweight in a farming region in South Africa. *Paediatric and Perinatal Epidemiology* 21, 432-440.
- JACKSON, D., CHOPRA, M. D., TANYA M, COLVIN, M. S. E., LEVIN, J. B., WILLUMSEN, J. F., GOGA, A. E. & MOODLEY, P. 2007b. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1. *AIDS*, 21, 509-516.
- JONES, L. L., GRIFFITHS, P. L., ADAIR, L. S., NORRIS, S. A., RICHTER, L. M. & CAMERON, N. 2008. A comparison of the socio-economic determinants of growth retardation in South Africa and Filipino infants. *Public Health Nutrition*, 11, 1220-1228.
- KRUSKAL, W. H. & WALLIS, W. 1952. Use of ranks in one-criterion variance analysis. *Journal of the American Statistical Association*, 47, 583-621.
- LABADARIOS, D. 2008. *National Food Consumption Survey: Fortification Baseline (NFCS-FB) South Africa, 2005*. Pretoria: National Department of Health, South Africa.
- LEPAGE, P., MSELLATI, P., HITIMANA, D.-G., BAZUBAGIRA, A., VAN GOETHEM, C., SIMONON, A., KARITA, E., DEQUAE-MERCHADOU, L., VAN DE PERRE, P. & DABIS, F. 1996. Growth of human immunodeficiency type-1 infected and uninfected children: a prospective cohort study in Kigali, Rwanda, 1988 to 1993. *The Pediatric Infectious Disease Journal*, 15, 479-485.
- LITTLE, R. J. A. & RUBIN, D. B. 1987. *Statistical analysis with missing data*, New York, Wiley.
- MASAKA, M., KASONGA, L., CHISENGA, M., SINKALA, M., CHINTU, C., TOMKINS, A. & FILTEAU, S. 2007. Early growth of infants of HIV-infected and uninfected Zambian women. *Tropical Medicine and International Health*, 12, 594-601.

- MCCOY, D., BESSER, D. & CHOPRA, M. 2002. Good Start Study protocol. Cape Town: Health Systems Trust and University of the Western Cape.
- MCMURRAY, C. 1996. Cross-sectional anthropometry: what can it tell us about the health of young children? . *Health Transition Review*, 6, 147-168.
- NATIONAL DEPARTMENT OF HEALTH. 2009. *Integrated nutrition programme* [Online]. Available: <http://www.doh.gov.za/programmes/inp/status.htm> [Accessed August 2009,].
- PATEL, D., BLAND, R., COOVADIA, H., ROLLINS, N., COUTSOUDIS, A. & NEWELL, M.-L. 2009. Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children *AIDS*, 24, 1-9.
- PATEL, D., BLAND, R., COOVADIA, H., ROLLINS, N., COUTSOUDIS, A. & NEWELL, M.-L. 2010. Breastfeeding, HIV status and weights in South African children: a comparison of HIV-exposed and unexposed children *AIDS*, 24, 1-9.
- PHILLIPS, R. S., ENWONWU, C. O., OKOLO, S. & HASSAN, A. 2004. Metabolic effects of acute measles in chronically malnourished Nigerian children. *The journal of nutritional biochemistry*, 15, 281-288.
- POLLOCK, H., GLASBERG, H., LEE, E., NIRENBERG, A., DAVID, R., KRASINKI, K., BARKOWSKY, W. & OBERFIELD, S. 1997. Impaired early growth of infants perinatally infected with human immunodeficiency virus: correlation with viral load. *The Journal of Pediatrics*, 130, 915-922.
- RAO, J. N. K. & SCOTT, A. J. 1981. The Analysis of Categorical Data From Complex Sample Surveys: Chi-Squared Tests for Goodness of Fit and Independence in Two-Way Tables. *Journal of the American Statistical Association*, 76, 221-230
- SALOOJEE, H. & DE MAAYER, T. 2007. What's new? Investigating risk factors for severe childhood malnutrition in a high HIV prevalence South African setting. *Scandinavian Journal of Public Health*, 35, 96-106.
- SANDERS, D., REYNOLDS, L., ELEY, B., KROON, M., ZAR, H., DAVIES, M., WESTWOOD, T., NONGENA, P. & VAN HEERDEN, T. 2007. Decreasing the Burden of Childhood Disease. *Western Cape Burden of Disease Reduction Project*.
- SCHAIBLE, U. E. & KAUFMANN, S. H. E. 2007. Malnutrition and infection: complex mechanisms and global impacts. *PLoS Medicine*, 4, 806-812.
- SCRIMSHAW, N. S. & SANGIOVANNI, J. P. 1997. Synergism of nutrition, infection and immunity: an overview. *The American Journal of Clinical Nutrition* 66, 464S-77S
- SCRIMSHAW, N. S., TAYLOR, C. E. & GORDON, J. E. 1968. Interactions of nutrition and infection. Monograph. Geneva: World Health Organisation.
- SIEGEL, S. & CASTELLAN, J. 1988. Two independent samples. In: ANKER, A. D. (ed.) *Nonparametric statistics for the behavioral sciences: second edition*. McGraw-Hill Book Company.
- STEYN, N. P., LABADARIOS, D., MAUNDER, E., NEL, J. & LOMBARD, C. 2005. Secondary anthropometric data analysis of the national food consumption survey in South Africa: The double burden *Nutrition*, 21, 4-13.
- TAYLOR, C. E. 1983. Synergy among mass infections, famines and poverty. *Journal of interdisciplinary history*, 14, 2483-501.
- THE EQUITY PROJECT 2001. Primary health care in the Eastern Cape Province: 1997-200. Pretoria: The EQUITY Project.
- THE LANCET 2006. Global child malnutrition. *The Lancet*, 367, 1459.
- THE PRESIDENCY. 2009. *Address by President Jacob Zuma on the occasion of World AIDS Day, Pretoria Showgrounds* [Online]. Available: <http://www.info.gov.za/speeches/2009/09120112151001.htm> [Accessed 15 March 2010].


- TWISK, W. R. 2003. *Applied longitudinal data analysis for epidemiology: A practical guide* United Kingdom: Cambridge University Press.
- UNAIDS 2010. *Survival of children HIV-infected perinatally and through breastfeeding a pooled analysis of individual data from resource-constrained settings*. Geneva, Switzerland UNAIDS.
- UNICEF 1998. *The state of the world's children*. New York: UNICEF.
- UNICEF 2004. *Progress for children: a child survival report card* New York: UNICEF.
- UNICEF 2007. *The state of the world's children* New York: UNICEF.
- UNICEF 2009. *The state of the world's children 2009: maternal and newborn health* New York: UNICEF.
- UNITED NATIONS. 2000. *Resolution adopted by the General Assembly* [Online]. Available: <http://www.un.org/millennium/declaration/ares552e.htm> [Accessed July 2009,].
- VIOLARI, A., COTTON, M. F., GIBB, D. M., BABIKER, A. G., STEYN, J., MADHI, S. A., JEAN-PHILIPPE, P. & MCINTYRE, J. A. 2008. Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine*, 359, 2233-2244.
- WILCOXON, F. 1945. Individual Comparisons by Ranking Methods. *Biometrics Bulletin*, 1, 80-83.
- WORLD BANK. 2009. *Poverty analysis-Measuring Inequality* [Online]. Available: <http://go.worldbank.org/3SLYUTVY00> [Accessed July 2009,].
- WORLD BANK INSTITUTE 2007. Health Outcome #2: anthropometrics. In: O'DONNELL, O., VAN DOORSLAER, E., WAGSTAFF, A. & LINDELOW, M. (eds.) *Analyzing Health Equity Using Household Survey Data: A Guide to Techniques and their Implementation*. Washington D.C: World Bank Institute.
- WORLD HEALTH ORGANIZATION 1995. Physical status: the use and interpretation of anthropometry. *World Health Organization Technical Report.854*.
- WORLD HEALTH ORGANIZATION. 2008. *Water related diseases* [Online]. Available: http://www.who.int/water_sanitation_health/diseases/malnutrition/en/ [Accessed August 2008 2008].
- ZERE, E. & MCINTYRE, D. 2003. Inequalities in under-five child malnutrition in South Africa. *International Journal for Equity in Health*, 2, 7.

APPENDICES

Appendix a: Ethics Approval for Good Start Study



Appendix b: Ethics Approval for secondary study

 **UNIVERSITY OF CAPE TOWN**
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Faculty of Health Sciences
Ruweida Joseph
Postgraduate Administrative Officer
Room N2.19, Wernher & Beit Building North
Anzio Road
Observatory, 7925
Tel: +27 21 406 6327
Fax: +27 21 406 6584
Email: Ruweida.Joseph@uct.ac.za

18 February 2009

V Ramokolo
824 Thrush Street
East Bank
Alexandra
2090

RMKVUN001

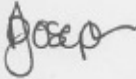
Dear Mr Ramokolo

Candidature approval

Degree	MPH
Title	Growth of children according to maternal and child HIV-1 status, related socio-economic characteristics and feeding practices: A prospective cohort study in 3 different settings in South Africa
Department	Public Health & Family Medicine
Supervisor	Dr B Draper
Ethics Approval	N/A

I am pleased to advise that the Chair of the Dissertations Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval will be obtained by publication in the next Dean's Circular.

Sincerely


Ruweida Joseph
Postgraduate Administrative Officer

