ANTIRETROVIRAL THERAPY IN HIV INFECTED CHILDREN- A SECONDARY ANALYSIS OF GROWTH PARAMETERS ASSOCIATED WITH AGE AT INITIATION

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Declaration

I, Lethabo Machaba-Simelani, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…….

16…… ……..day of……November 2018.

Dedication

This work is dedicated to my family: the Machaba and Simelani family (my husband and two children). Thank you for being the pillars I can lean on.

‘I look up to the mountain, from whence cometh my help?... My help cometh from the Lord’ Psalm 121 v 1-2

Presentations Arising from this Work

Poster Presentation at the 19th International Workshop on HIV Observational Database. Catania, Sicily 26th-28th March 2015.

Title of Presentation:

Antiretroviral therapy in HIV-infected children- A secondary analysis of growth parameters associated with age at initiation.

Abstract

Introduction: Growth failure in HIV infected children is a significant identifiable complication of HIV and can present as stunting, weight loss and or severe acute malnutrition (SAM). A description of the response of growth to ART initiated in young children is presented. **Methods:** A secondary data analysis of a prospective cohort of 292 HIV-infected children less than 3 years of age initiated on ART at a Johannesburg HIV Clinic between January 2004 and 31 August 2010 was done. Comparison of growth parameters for the time points 12, 24 and 36 months after initiation of ART was done in relation to age, gender, year of initiation, underweight for age (UWA), stunting or wasting at ART initiation. **Results:** At ART initiation, almost half the children were UWA (55%), 62% were stunted and 25% were classified as wasted The recovery of weight-for-age Z-score (WAZ) and weight-for-height Z-score (WHZ) was much faster than the recovery of height-for-age Z-score (HAZ), however, analysis of all growth parameters showed a plateau of growth recovery after 3 years of follow-up. Lower WAZ was noted at initiation when compared to HAZ. UWA was more common in young children whereas stunting was more common in older children. Improvement after 3 years of follow up was noted for both weight and height but recovery of HAZ did not reach the population median as closely as WAZ did. **Conclusion:** ART has a positive effect on the over-all growth of HIV-infected children. Age at initiation of ART was not the most important in supporting when to start ART, but having a Z-score <-2 was found to be critical. Despite sustained growth response and catch up growth in HIV-infected children on ART, normal weights and heights were not achieved after 3 years.

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Table of Contents

Declaration……II
Dedication……III
Presentations……..IV
Abstract……V
Acknowledgements……..VI
Table of Content……VII
List of figures……IX
List of Tables……X
Nomenclature……..XI
1 Chapter 1: Introduction……..1
1.1 The HIV pandemic in South Africa……..1
1.2 Growth Failure in HIV-infected Children 2
1.3 WHO description of Growth..... 2
1.4 Impact of Anti-retroviral therapy on Growth..... 4
1.5 South African HIV Guidelines..... 5
1.6 Importance of this study 6
2 Chapter 2: Study Objectives 8
2.1 Objectives 8
2.2 Null Hypothesis 8
3 Chapter 3: Methods 9
3.1 Study Design:..... 9
3.2 Study Population 9
3.3 Data Domain: 10
3.4 Statistical Methods 12
3.5 Ethical Considerations 13
3.6 Funding 13
4 Chapter 4: Results 14

4.1 Study population and baseline Characteristics..... 14
4.2 Growth Response 22
4.2.1 Weight- for-Age……22
4.2.2 Height for Age..... 26
4.2.3 Weight-for-Height 29
5 Chapter 5: Discussion..... 32
6 Conclusion……40
7 Recommendations.……41
8 References..... 42
10 Appendix 1- Patient Consent form……46
11 Appendix 2- WITS Research and Ethics Committee Clearance Certificate……..…47
12. Appendix 3 - Rahima Moosa Hospital Superintendent Consent……. ……...48
13. Turnitin Report……..49

List of Figures

Figure 1.1: HIV prevalence in South Africa 2012……1
Figure 3.1: Inclusion and exclusion criteria for study population at RMMCH..... 10
Figure 4.1: Overview of study population 15
Figure 4.2: Number of children initiated yearly on ART at Empilweni HIV Clinic 15
Figure 4.3: Distribution of age of WAZ at baseline...……...18
Figure 4.4: Distribution of age of HAZ at baseline...……18
Figure 4.5: Distribution of age of WHZ at baseline...……19
Figure 4.6: Growth Comparison of WAZ at ART Initiation...……25
Figure 4.7: Growth Comparison of WAZ at ART Initiation...……25
Figure 4.8: Growth Comparison of HAZ at ART Initiation..……28
Figure 4.9: Growth Comparison of HAZ at ART Initiation..……..28
Figure 5.0: Growth Comparison of WHZ at ART Initiation…...……31
Figure 5.1: Growth Comparison of WHZ at ART Initiation..……31

List of Tables

Table 4.1: Pre-Treatment Characteristics of Children initiatd on ART at RMMCH 20

Table 4.2: Pre-Treatment Characteristics of Children initiated on ART at RMMCH…...21

Table 4.3: Median(IQR) WAZ at Baseline, 12months, 24months and 36 after ART Initiation..... 24

Table 4.4: Median(IQR) HAZ at Baseline, 12months, 24months and 36 after ART Initiation……...27

Table 4.5 Median(IQR) WHZ at Baseline, 12months, 24months and 36 after ART Initiation……..……30

Nomenclature

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CDC	Centers for Disease Control and Prevention, USA
DOH	Department of Health
HAZ	Height-for-age Z-score
HIV	Human Immunodeficiency Virus
HRCS	Human Resource Science Council
RMMCH	Rahima Moosa Mother and Child Hospital (previously Coronation Women and Child Hospital)
WHO	World Health Organization
WAZ	Weight-for-age Z-score
WHZ	Weight-for-Height Z-score
UWA	Underweight for age

Chapter 1: Introduction

1.1 The HIV pandemic in South Africa

The Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) pandemic has had its greatest impact in Africa, with an estimated 7.1 million adults and children living with HIV at the end of 2016.[1] In South African children, infection with HIV is still a great cause of morbidity and mortality with 320,000 children estimated to be living with HIV at the end of 2016. An estimated 1.7 million children were also orphaned due to HIV by 2016.[1] The numbers reported above have increased when compared to those released by the Human Science Research Council (HSRC) in 2012, who reported an estimated 6.4 million people living with HIV in South Africa in 2012.[2] Further results from this HSRC report also indicated that children contributed significantly to the South African overall burden of HIV (Figure 1).[2]

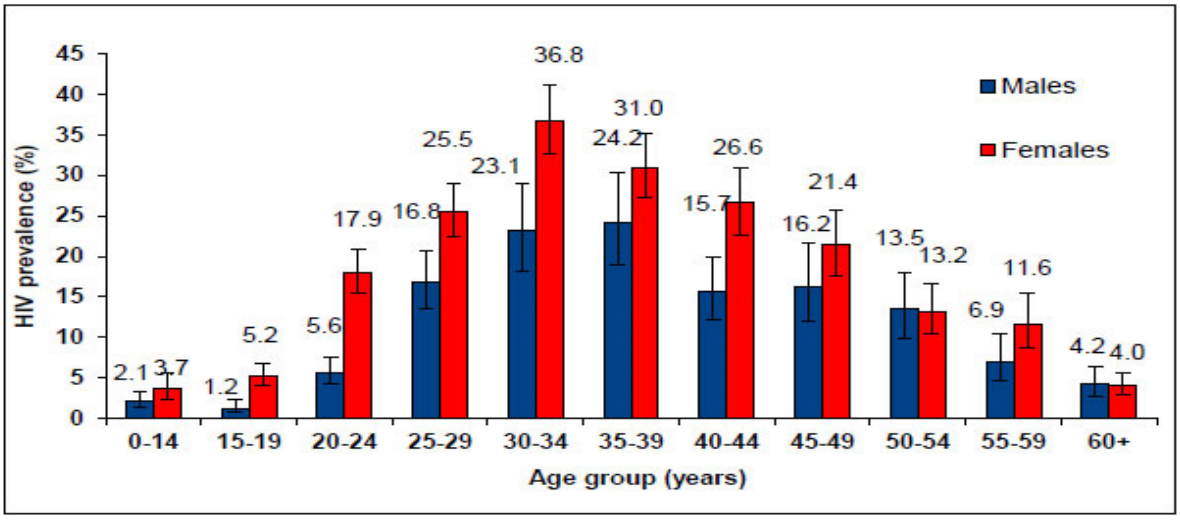

Figure 1.1: HIV prevalence in South Africa 2012

1.2 Growth Failure in HIV-infected Children

Growth abnormalities are one of the biggest causes of morbidity in HIV-infected children.[4] Growth failure can present as stunting, weight loss and or severe acute malnutrition with a poor response to nutritional rehabilitation.[4] The mechanisms of growth failure in this group of children are complex and include genetic and environmental factors such as poor nutrition, low socioeconomic status and infection by different pathogens including perinatally acquired infections.[4] Other factors that can contribute to this growth failure are changes in metabolic and endocrine function related to HIV infection.[5] Many studies in Africa have demonstrated that poor growth is a sensitive indicator of HIV disease progression.[6] One such study done in Uganda, showed that HIV-infected children who had more severe disease: stage II, III, IV before initiation of treatment were 1.5 times more likely to become underweight (OR 1.51, CI 1.07-2.14).[7] A study in Lilongwe, Malawi, demonstrated that both the baseline weight-for-age Z-score (WAZ) and the height-for-age Z-score (HAZ) were the most important determinants of growth trajectories of HIV-infected children on antiretroviral therapy (ART).[8]

1.3 WHO description of Growth

The World Health Organisation (WHO) Multicentre Growth Reference Study was implemented between 1997 and 2003 with the purpose of designing a standard of growth for children. Deviations from this normal pattern of growth can thus be described as abnormal.[9] The growth standards derived from this study have provided us with a tool that describes good physiological growth in children less than five years of age. The WHO standard aimed at replacing the US National Centre for Health Statistics (NCHS) growth reference which had been criticized for its lack of universal applicability and not reflecting

the growth of breastfed infants enough.[10] In 1997 – 2003, the WHO standards were tested in 6 different countries before being recommended and were based on the infant grown by a mother's milk.[10] Of significance, some of the countries included in the study were developing countries like South Africa, namely: Brazil, Ghana, India.[10]

To assess growth, the WHO has adopted the Z-score system as a means for analysis and presentation of anthropometric data. This system allows a child or group of children to be compared to a reference population. The Z-score system allows for the expression of the anthropometric value as a number of standard deviations (SD) or Z-scores below or above the reference mean or median, thus allowing for the following definitions of poor growth.[9]:

- Decreased HAZ (stunting): -2 SD below the mean (0).
- Decreased WAZ (underweight for age, UWA): -2 SD below the mean (0).
- Decreased WHZ (wasting): -2 SD below the mean (0).
- Severe acute malnutrition (SAM), wasting: WHZ -3SD below the mean(0).[9]
- Severe stunting: -3 SD below the mean (0).
- Severe UWA: -3 SD below the mean (0).

Growth in HIV-infected children has long been regarded as being of great importance as displayed by the universal inclusion of growth abnormalities as a criterion for severe disease in both Centers for Disease Control and Prevention (CDC) and WHO classification systems. Several studies done in the United States of America on HIV-infected children have shown that normal WAZ was reached within a year of ART initiation, whilst HAZ normal parameters were attained within 2 years of ART initiation.[11]

1.4 Impact of Anti-retroviral Therapy on Growth

It has been shown that access to antiretroviral therapy (ART) in low and middle-income countries increased from 400,000 in 2003 to 6.65 million in 2010 which resulted in a decreased number of people dying from AIDS.[3] More updated South African statistics reported that there were 3.9 million people living with HIV and on treatment in 2016.[1] The introduction of ART in developing countries has also played an important role in the improvement of not only growth, but also more importantly, in the survival of children infected with HIV.[11] One such improvement is specific to Sub-Saharan Africa, where recent studies have reported that, despite the high prevalence of growth failure in HIV-infected children, there is significant weight gain and increase in height that occurs after initiation of ART.[12] Results from a study in Uganda showed that the mean increase in WAZ and HAZ in children initiated on ART was from -0.98 (1.7SD) to +1.22 (1.2SD) and –1.99 (1.7SD) to +0.76 (2.4SD) respectively.[12] The Children with HIV Early Antiretroviral Therapy (CHER) trial also supports early initiation of ART. Their findings showed early ART reduced infant mortality by 76% and HIV progression by 75%.[13]

Despite the implementation of programs to improve access to ART, South Africa is still encountering vast challenges with the effect that the HIV pandemic is having on people's lives every day.[3] The question often asked is: Does age at initiation of ART have a positive influence on growth? Several African studies mentioned above, have answered "yes" to this question as they have indicated that earlier age at initiation of treatment has a positive effect on growth.[7,8,11] However, ART-related improvements in WAZ have been shown to occur before improvements in HAZ. [7] The long-term consequences of HAZ (stunting)

below normal levels remain unclear. Not much is also known about sex differences in growth response to ART in HIV-infected children.[14]

1.5 South African HIV Guidelines

In 2004 South Africa formulated HIV treatment guidelines to ensure optimal therapy and good clinical outcomes. Part of guidelines also included follow-up visits during which weight, height and head circumference must be recorded and plotted on growth charts.[14]

In the 2004 guidelines first-line therapy included two Nucleoside Reverse Transcriptase Inhibitors (NRTI: stavudine [d4T] and Lamivudine [3TC]), together with either a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) in children three years or older or a Protease Inhibitor (PI) in children less than three years old.[15] The criteria for starting ART included both medical and psychosocial criteria. Medical criteria included: modified WHO stage 3 or 4 disease; or children with CD4 percentage less than 20% in children under 18 months old; and CD4 less than 15% in children over 18months. The psychosocial criteria mainly included an identifiable and reliable adult able to administer ART and who has disclosed to another adult living in the same house.[14]

In 2008 the guidelines were further modified. All children with WHO stage 3 or 4 disease were to be started on treatment irrespective of age. Immunological criteria for starting ART were age based:

1. Children less than 1 year: CD4 < 35 %
2. 1-5 years: CD4 < 20%
3. > 5 years: CD4 < 15%.[15]

The psychosocial criteria were similar to those in 2004 and the same drugs were used.[15] Due to the side-effect profile of d4T, especially lipodystrophy and other mitochondrial side effects, abacavir (ABC) was introduced in place of d4T as first line therapy in 2010.[16] Guidelines for the eligibility of ART were also further modified in 2010: all children less than one year of age qualified for ART, children between one and five years of age could receive ART if their CD4 was less than 750 absolute count or 25%; those greater than five years of age qualified for ART if CD4 was less than 350; WHO stage 3 or 4 diseases was a criteria for all ages.[16]In 2013, new guidelines recommended that all children under five years of age qualified for treatment regardless of CD4 count.[17] Children older than five years of age qualified if their CD4 was less than 350 or if they were WHO stage three or four.[17] In September 2016, a Universal Test and Treat Strategy was implemented and recommended that all HIV-infected people be started on ART irrespective of clinical or immunological status. The changes in the guidelines over time would likely affect the baseline characteristics of children initiating ART and should therefore be taken into account when analyzing the growth response of children to ART initiation. The South African guidelines have also been noted to strive towards enabling earlier and earlier initiation of ART in HIV-infected children.

1.6 Importance of this study

It is important that we know and are able to describe the changes in the following growth parameters in HIV-infected children following initiation of ART: WAZ, HAZ and WHZ. Another question that needs to be answered is how age at initiation and growth status at initiation of ART influences these growth parameters as treatment proceeds. The first years of life are important in providing a child with a good growth foundation and also in

ensuring normal growth later in life. This study therefore also looks at the effect of a younger age at ART initiation on growth.

Chapter 2: Study Objectives

Objectives

1. Describe the change of WAZ, HAZ and WHZ between initiation and at 12, 24, and 36 months post ART.
2. Describe the effects of age at initiation of ART: (stratified into four groups as less than 6 months, 6-12; 12-24 months and 24-36 months), on the growth change in objective 1.

Null Hypothesis

Age at initiation of ART does not affect the improvement in growth parameters in the first 3 years of treatment in HIV-infected Children.

Chapter 3: Methods

3.1 Study Design:

This study is a retrospective secondary analysis of a prospective cohort of HIV infected children attending Empilweni HIV Clinic, which is part of Rahima Moosa Mother and Child Hospital.

3.2 Study Population

Empilweni Clinic has lived up to the meaning of its name: “where there is life”. To date there have been more than 4000 children initiated on ART and an estimated 1600 children actively attending the clinic. All children at this site are HIV-infected and are managed in accordance with the South African HIV National guidelines. Enrolment of children onto ART at this site is in line with the national roll-out of ART which begun in 2004 and is still ongoing allowing a database of those initiated on ART to be established. De-identified data of patients from the beginning of 2004 until 31 August 2010, was extracted from this existing database and was used for this study. Patients lost to follow-up, transferred out or those who died were not included in this study as they did not meet the inclusion criteria. (See figure 3.1)

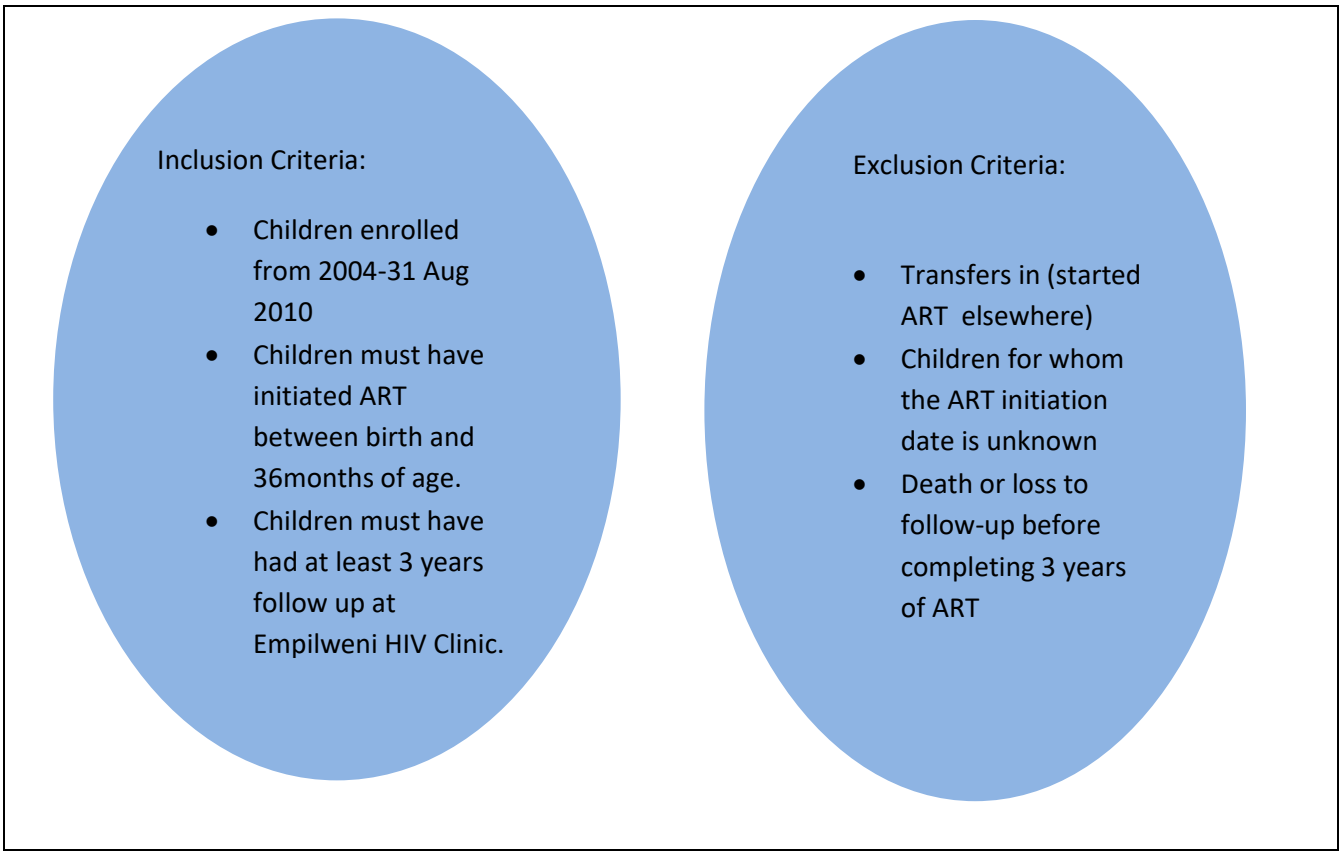

Figure 3.1: Inclusion and exclusion criteria for study population at RMMCH.

3.3 Data Domain:

The following patient characteristics were extracted from the database created at Empilweni Clinic:

1. Age at ART initiation
2. Gender
3. WAZ (weight-for-age at baseline, 12, 24 and 36 months)
4. HAZ (height-for-age at baseline, 12, 24 and 36 months)
5. WHZ (weight-for-height at baseline, 12, 24 and 36 months)

The Z-score was chosen as a favorable measure of growth in this study as it represents normal growth pattern as that of a breastfed infant and also the study from which it was generated from included other developing countries like Ghana, India and Brazil. The baby friendly initiative in South Africa promotes breastfeeding as the best form of feeding practice. Information on feeding practice was not available in the database. Due to the provision of free replacement milk to HIV-positive mothers in the first six months after delivery, our population likely presented a mix of infant formula and breastmilk consumption.

Baseline values were taken as the measure closest to the date of ART initiation from two months before to one week after initiation of ART. Values for 12, 24 and 36 months were taken from a window of two months around those time points for each patient to allow consistency. If there was more than one value in a window, the one closest to the 12, 24 and 36 month time points was chosen. The categories were defined as:

- 0-≤6
- >6-≤12
- >12-≤24
- >24-≤36
- i.e. 12.0000 is in the 6-12 group

Z-scores were calculated for weight-for-age, height-for-age and weight-for-height in accordance with the World Health Organization growth standard from 2007 using SAS version 9.3 (Cary, North Carolina, USA). Apart from actual values the following categories were created:

- Decreased HAZ (stunting): -2SD below the mean (0)
- Decreased WAZ (underweight): -2SD below the mean (0)
- Decreased WHZ (wasting): -2SD below the mean(0).[9]

Data cleaning was done for variables that were outliers to the normal distribution of variables. The variables concerned were re-checked by pulling out master files from records, verifying recorded growth parameters and correcting errors. These were largely data capturing errors. This validation was made possible as each anthropometric measurement was recorded for every child with each visit and questionable parameters were excluded or corrected.

3.4 Statistical Methods

The results captured were entered into a Microsoft Office Excel database. A separate database was extracted from the main database which did not contain patient identifiers other than a study number.

Basic statistical methods were used to analyze the data. Continuous variables were documented as median and inter-quartile range. The median was used in preference to the mean as variables did not always show a normal distribution. Categorical variables were presented as frequencies and proportions.

The above mentioned generated Z-scores taken for the 12, 24 and 36 months of age at initiation groups were compared using the Chi-Square test for categorical variables. The continuous parametric variables were compared using ANOVA and t-tests for the 12, 24 and 36 months of age at initiation groups. Those variables which were non-parametric

were compared using the Wilcoxon signed-rank test. All statistical comparisons were assessed for statistical significance at the alpha=0.05 level.

3.5 Ethical Considerations

Empilweni Clinic has an existing ethics approval for the analysis of routine data and all patients were invited to sign a consent form for the use of their data (Appendix 1). Patients/caregivers who opted not to have their data included were excluded from the analysis. Parents had to sign, as children were minors. Only de-identified data was extracted from the existing database at Empilweni HIV Clinic into a Microsoft Excel sheet and permission to use the data was obtained from the clinic's Gate-Keeper. Written permission was obtained from the Medical Superintendent at Rahima Moosa Hospital (Appendix 3).

Permission to proceed with this study was approved by the Post Graduate Committee of the University of the Witwatersrand. The same proposal was also submitted to the Human Research Ethics Committee of the University of Witwatersrand who granted permission for this data review to be done (Appendix 2).

3.6 Funding

This project needed minimum funds to cover printing costs and transportation to RMMCH. This was self-funded.

Chapter 4: Results

4.1 Study Population and Baseline Characteristics

The selection of children and how they played a role in the analysis is demonstrated in Figure 4.1. From the start of Empilweni HIV Clinic in 2004 there were a total of 3491 children started on ART between January 2004 and 31 August 2010. Of these 3491 children, 292 met inclusion criteria for this study. To perform the growth analysis, these children were divided into 4 groups by age at initiation of ART:

- <6 months (n=63),
- 6-12 months (n=69),
- 12-24 months (n=92),
- 24-36 months (n=68).

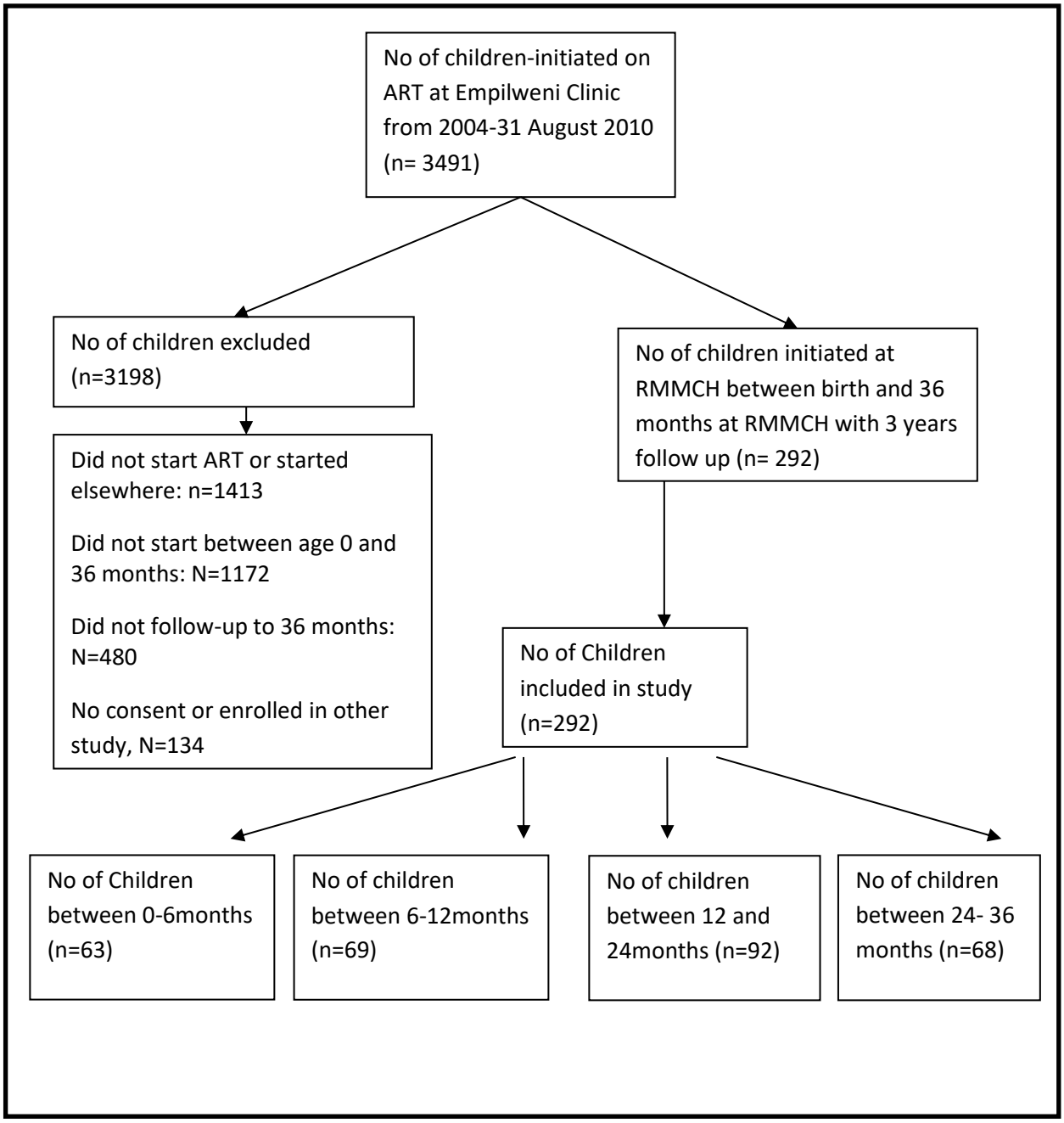

Figure 4.1 Overview of study population. The population reviewed was HIV-positive children at Empilweni clinic at RMMCH enrolled from January 2004 until 31 August 2010. These children were all initiated on ART between birth and 36 months of age, with age cut offs being based on age of initiation of ART as stipulated above.

The distribution of ART initiation year for the children included in this study is shown in Figure 4.2. It was noted that the year 2004 had the lowest percentage of children initiated on ART (5%), but the number of children initiated on ART increased thereafter with 2007 having the highest percentage of 20 %.

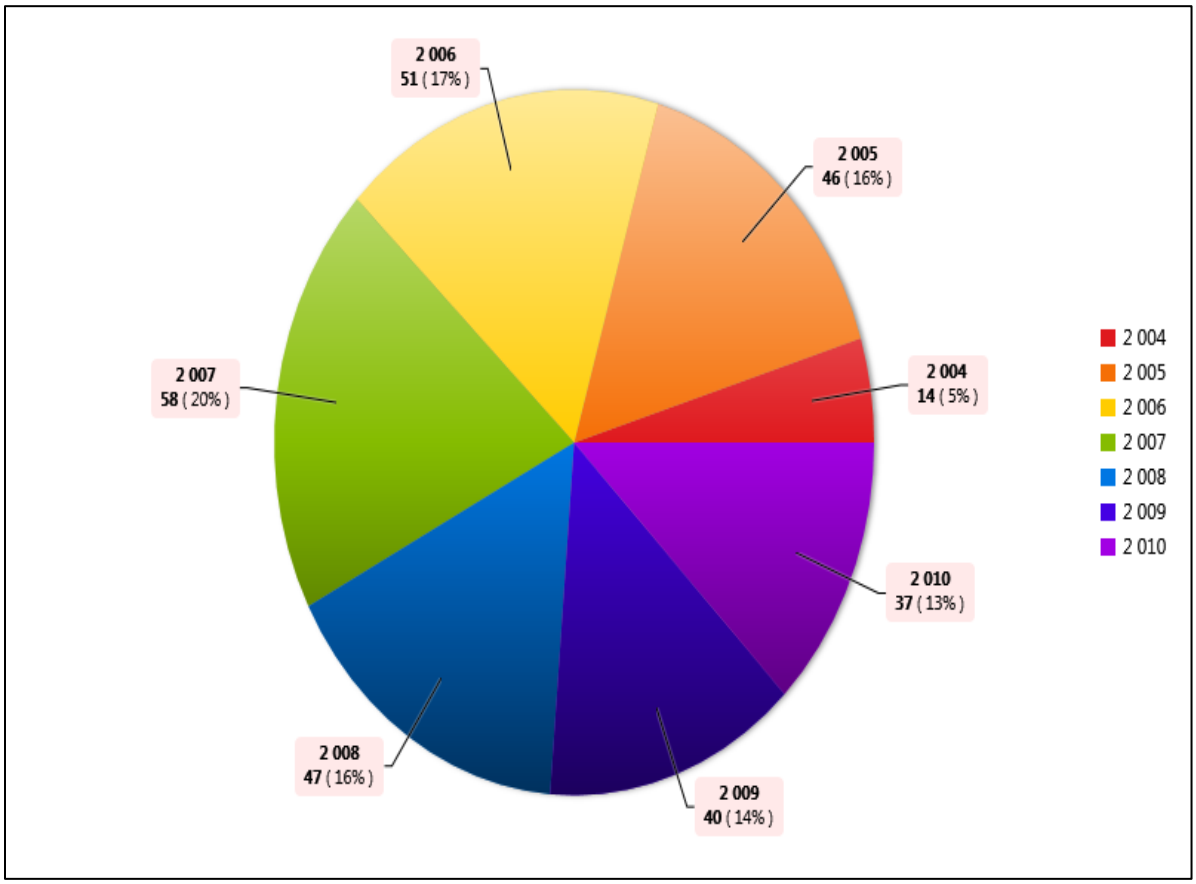

Figure 4.2: Number of children initiated yearly on ART at Empilweni HIV Clinic: Number of children's data evaluated between 2004 and 2010 at Empilweni HIV Clinic.

The characteristics of the 292 HIV-infected children who were initiated on ART from 2004 until 2010 are shown in Table 4.1. Almost half (58%) of the HIV-infected children in the study were initiated on ART between 2004 and 2007. At initiation, the median age of the children was 13.8 months (Interquartile range [IQR]: 7 to 23 months). A further illustration of the age distribution is shown in Figures 4.3, 4.4 and 4.5 displayed against WAZ, HAZ and WHZ distribution respectively. Close to half the HIV-infected children where underweight for age (55%), 62% were stunted and 25% were wasted.

When looking at year of initiation, it was noted that younger HIV-infected children (0-12 months) were more likely to be enrolled in the later years (2008-2010) and more older children (>12months) earlier (refer to table 4.2). Further analysis showed that underweight at initiation was equally common throughout the two eras (55% vs. 54%, p=0.91). Stunting at ART initiation was significantly more common in the earlier era (72% in2004-2007 vs. 51% in 2008-2010; p=0.0008), low WHZ was less frequent than underweight and stunting and significantly more common in the latter era (20% in 2004-2007 vs. 31% in 2008-2010; p=0.046).

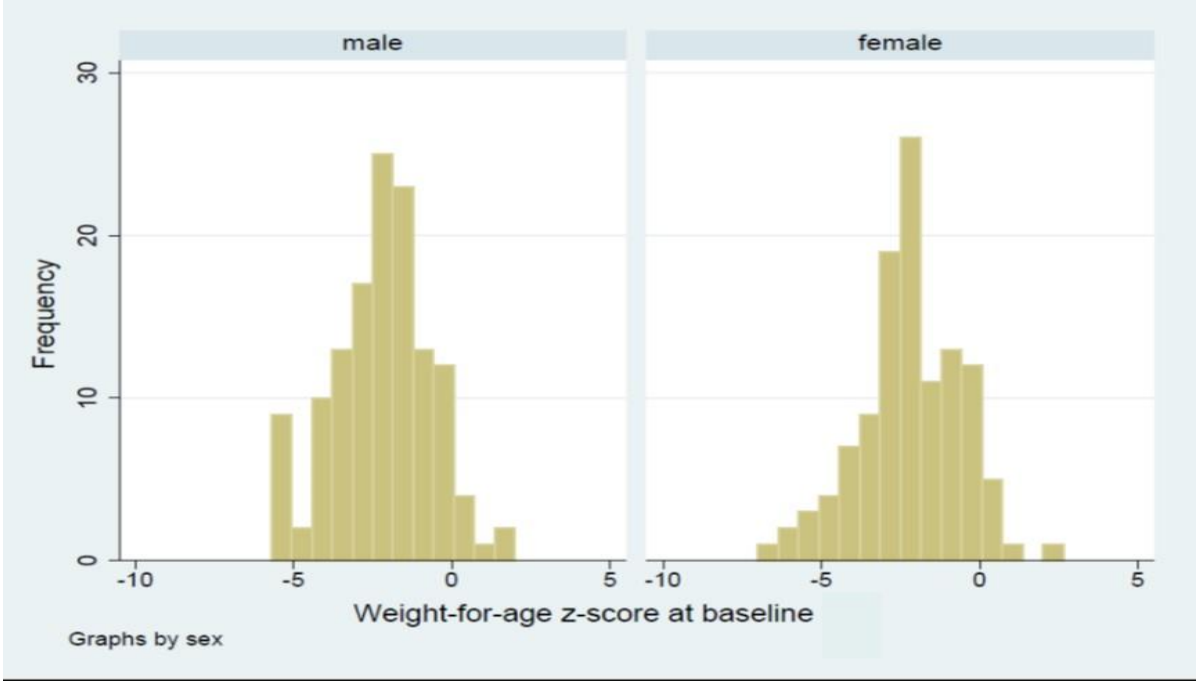

Figure 4.3 Distribution of age of WAZ at ART initiation

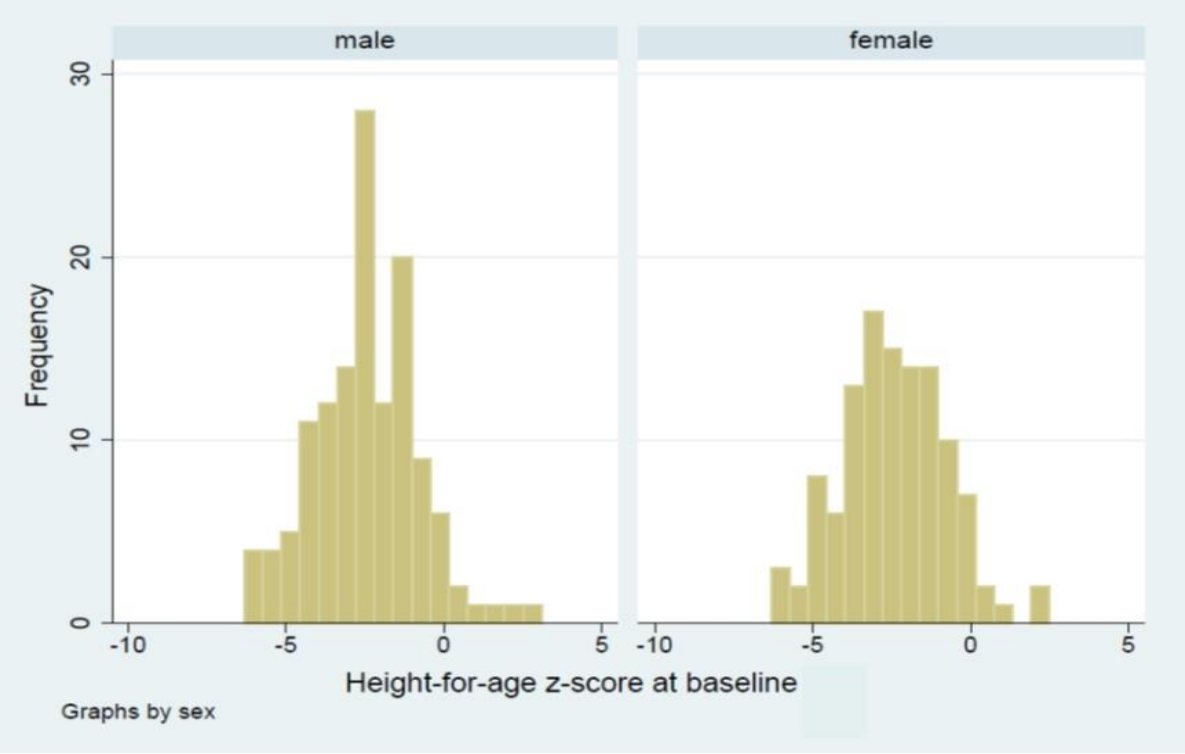

Figure 4.4 Distribution of age of HAZ at ART initiation

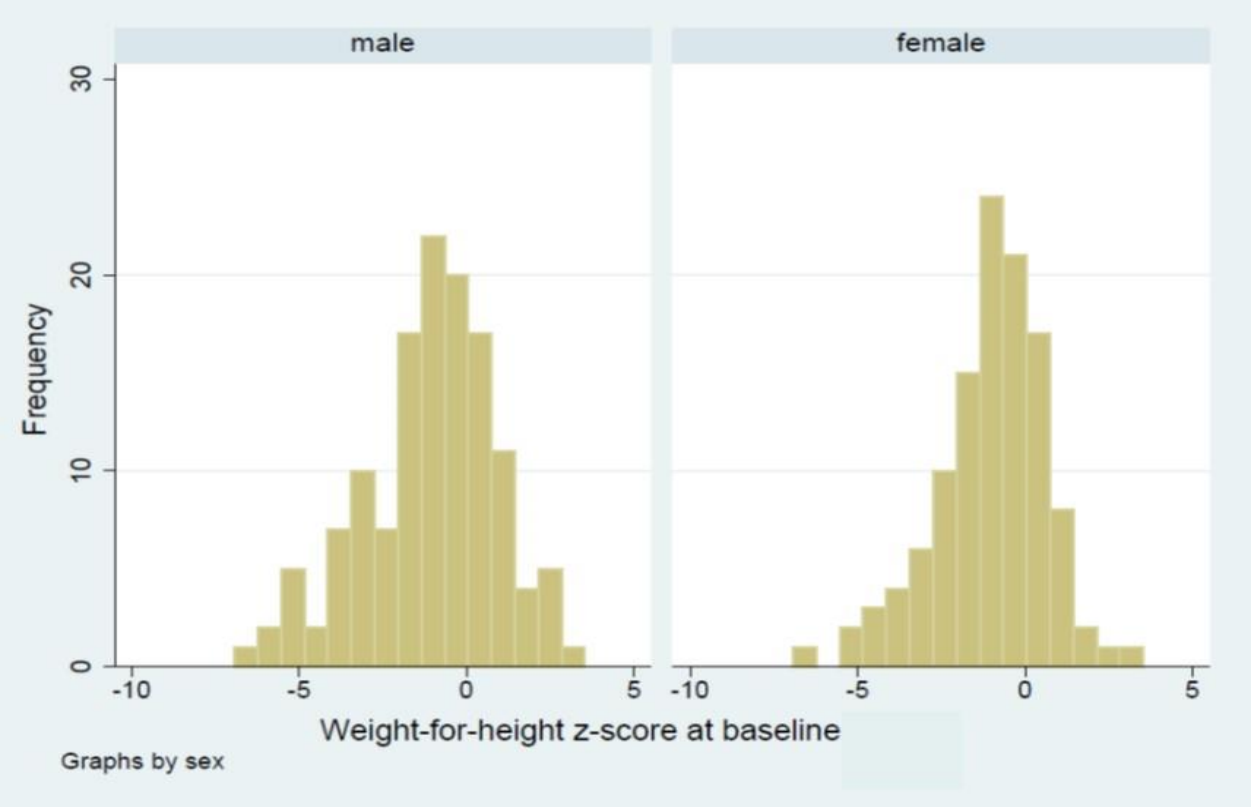

Figure 4.5 Distribution of age of WHZ at ART initiation

Table 4.1: The pre-treatment characteristics of children initiated on ART at RMMCH.

Baseline Characteristics	N (%)
All children	292
Median age in months (IQR)	13.8 (7,23)
0-6 months	63 (21)
6-12 months	69 (24)
12-24 months	92 (32)
24-36 months	68 (23)
Female sex	141 (48)
Underweight: WAZ < -2	135(55)*
Stunted: HAZ< -2	152 (62)*
Wasted: HAZ< -2	62 (25)*
Median WAZ (IQR)	-2.1(-3.3,-1.2)
Median HAZ (IQR)	-2.4(-3.6,-1.5)
Median WHZ (IQR)	-0.1(-2.1,0.2)

Table 4.1: All statistics are given as N (%) unless specified otherwise. * Denominator for baseline WAZ, HAZ and WHZ values was 246. WAZ= weight-for-age Z-scores, HAZ= height-for-age Z-scores, WHZ= weight-for-height Z-scores, IQR = Inter-quartile range.

Table 4.2: The pre-treatment characteristics of children initiated on ART at RMMCH.

	Total N of children pre-treatment	0 – 6 months	6-12 months	12- 24 months	24 – 36 months	P value
All children, N (row %)	292	63 (21)	69 (24)	92 (32)	68 (23)	0.81
Female	141 (48)	31 (49)	36 (52)	44 (47)	30 (44)	0.82
2004 – 2007, N (%)	169 (58)	31 (49)	30 (43)	67 (73)	41 (60)	0.0009
2008 – 2010, N (%)	123 (42)	32 (51)	39 (57)	25 (27)	27 (40)	
WAZ<-2 Z-score, N (%)	135 (55)*	35(67)	38 (67)	46 (59)	16 (26)	<0.0001
HAZ<-2 Z-score, N (%)	153 (62)*	23 (44)	35 (63)	62 (79)	33 (55)	0.0004
WHZ<-2 Z-score, N %)	62 (25)*	20 (38)	22 (39)	15 (19)	5 (8)	<0.0001

Table 4.2 shows the pre-treatment characteristics of children who were initiated on ART at RMMCH, Empilweni HIV Clinic. * The denominator for WAZ, HAZ and WHZ baseline values was 246. All percentages are column percentages unless otherwise indicated. WAZ= weight-for-age Z-scores, HAZ= height-for-age Z-scores, WHZ= weight-for-height Z-scores

4.2 Growth Response

4.2.1 Weight-for-Age

In terms of WAZ, there was a rapid increase in Z-scores in the first 12 months post-initiation of ART, followed by a more stable growth recovery thereafter. The median weight Z-scores increased from -2.2 (IQR: -3.1 to -1.2) at initiation to just below -0.7 (IQR: -1.4 to -0.1) at 12 months (Table 4.3). The subsequent plateau in growth is demonstrated by a fairly static median Z-scores at 24 months and 36 months, of -0.7 (IQR: -1.3 to -0.1) and -0.8 (IQR: -1.4 to -0.1) respectively. When stratified by age at initiation this difference in growth is noted mainly at initiation ($p<0.001$) but no longer noted by 12 months ($p=0.282$), 24 months ($p=0.38$) and 36 months ($p=0.37$).

Children who were underweight (WAZ<-2) and of normal weight (WAZ>-2) at ART initiation demonstrated an increase in WAZ in the first year of life, with a more rapid increase in weight for those UWA (Table 4.3 and Figure 4.7). The group with a WAZ-score >-2 at initiation, who also are the older children, had a smaller increase in Z-scores when compared to the UWA, as they started off at a better Z-score of -1.1 (IQR-1.5 to -0.3). There was a noticeable significant difference between the two groups (WAZ>-2 and WAZ<-2) at initiation of ART with regards to Z-scores, $p<0.001$, with a median Z-score of -1.1 (IQR -1.5 to -0.3) in children starting with WAZ>-2, compared to -3.0 (IQR -3.9 to -2.4) in children starting with WAZ<-2. Figure 4.7 demonstrates how both groups end up on fairly similar Z-scores after 3 years of follow-up having started far apart at initiation of ART.

When children were analyzed in terms of their age, children in the age categories <6 months and 6-12 months at ART initiation started off with worse growth parameters for

WAZ: -2.6 (IQR: -3.8 to -1.4) and -2.7 (IQR: -4.3 to -1.9) compared to children above 12 months, WAZ: -2.2 (IQR: -2.9 to -1.4) and -1.4 (IQR: -2.0 to 0.4;$p<0.001$), but also had a greater increase in WAZ within the first years. By 36 months, children aged <6 months and 6-12 months at initiation had gained 1.8 (IQR: 0.8 to 2.9) and 1.8 (IQR: 0.8 – 3.1) respectively whilst children aged 24-36 months at initiation only gained 0.6 (IQR: 0.0 to 1.3). The findings of this study, therefore, indicate that with regards to WAZ, age at initiation is significant in terms of the difference at baseline. Having a low Z-score is more common at a younger age. The final Z-score after three years of ART was not found to be significantly different when stratified by the age at initiation but remained different when stratifying by the Z-Score at initiation being <-2 SD vs >-2.0 SD ($p<0.001$). There was no significant difference in weight at initiation or after three years of ART when stratifying by gender ($p>0.05$).

Table 4.3 Median (IQR) WAZ at Baseline, 12 months, 24 months and 36 months after ART initiation:

	Baseline	WAZ at 12months	WAZ at 24months	WAZ at 36months
All Patients N=292	-2.2 (-3.1 to -1.2)	-0.7 (-1.4 to -0.1)	-0.7 (-1.3 to -0.1)	-0.8 (- 1.4 to – 0.1)
Males	-2.2(-3.3 to -1.2)	-0.7 (-1.3 to 0.1)	-0.6 (-1.2 to 0.1)	-0.7 (-1.3 to -0.1)
Females	-2.2(-3.1 to -1.1)	-0.7(-1.6 to -0.1)	-0.8 (-1.3 to -0.2)	-0.8(-1.5 to 0.1)
P -value 1	0.95	0.31	0.39	0.35
Initiation of ART in 2004-2007	-2.1 (-3.2 to -1.2)	-0.7 (-1.4 to 0.1)	-0.6 (-1.2 to -0.1)	-0.8(-1.3 to -0.1)
Initiation of ART in 2008 - 2010	-2.2 (-3.1 to -1.1)	-0.7 (-1.4 to 0)	-0.8(-1.5 to -0.2)	-0,7(-1.5 to -0.2)
P-value	0.44	0.89	0.28	0.55
Age category at initiation:				
0 – 6 months	-2.6 (-3.8 to -1.4)	- 0.6 (-1.3 to 0)	-0.9 (-1.3 to 0.4)	-0.9 (-1.5 to -0.1)
6- 12 months	-2.7 (-4.3 to -1.9)	-0.7 (-1.6 to -0.2)	-0.7 (-1.3 to -0.2)	-0.8 (-1.2 to -0.2)
12- 24 months	-2.2(-2.9 to -1.4)	-0.9(-1.5 to -0.2)	-0.7 (-1.5 to -0.2)	-0.7 (-1.6 to -0.3)
24 – 36 months	-1.4(-2.1 to -0.4)	-0.5(-1.3 to 0.2)	-0.6(-0.9 to 0.1)	-0.5(-1.1 to -0.02)
P-value	<0.0001	0.28	0.38	0.37
<-2 Z score	-3.0 (-3.9 to -2.4)	-0.9 (-1.8 to 0.3)	-0.9 (-1.5 to -0.3)	-1.0 (-1.6 to-0.4)
>-2 Z score	-1.1 (-1.5 to -0.3)	-0.4 (-1.0 to 0.5)	-0.5 (-0.9 to 0.3)	-0.4 (-1.1 to O.1)
P-value	<0.0001	<0.0001	0.0003	<0.0001

Table 4.3 Medians are listed with IQR=Inter-quartile range

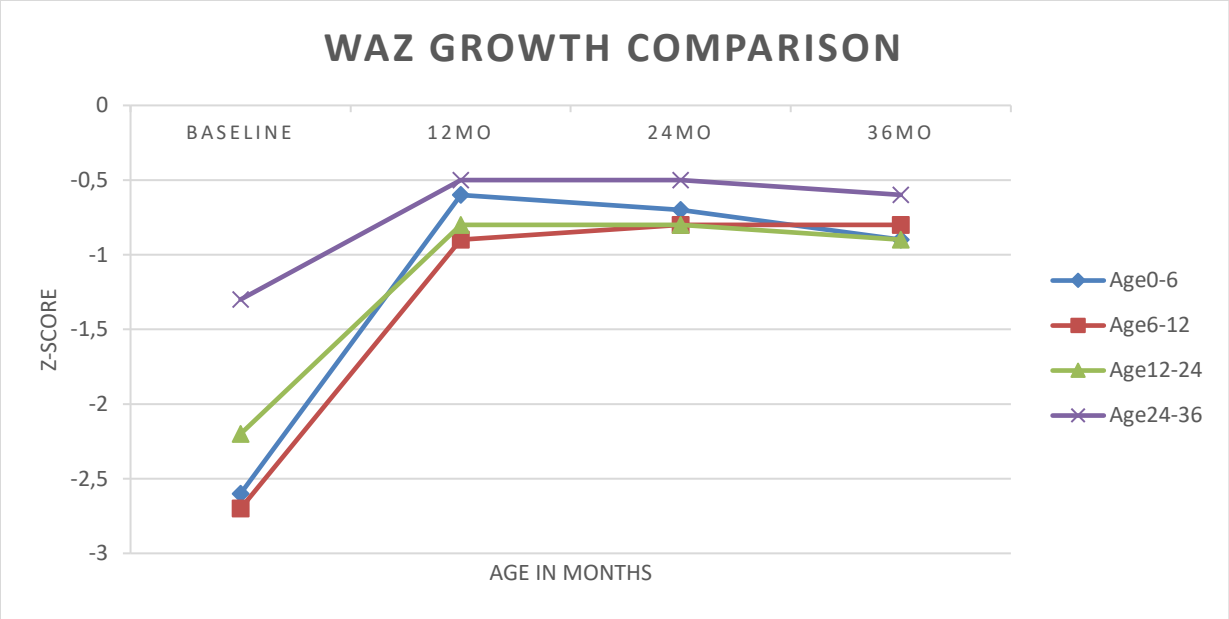

Figure 4.6 Growth Comparison of WAZ at ART Initiation and at 12, 24 and 36 months.

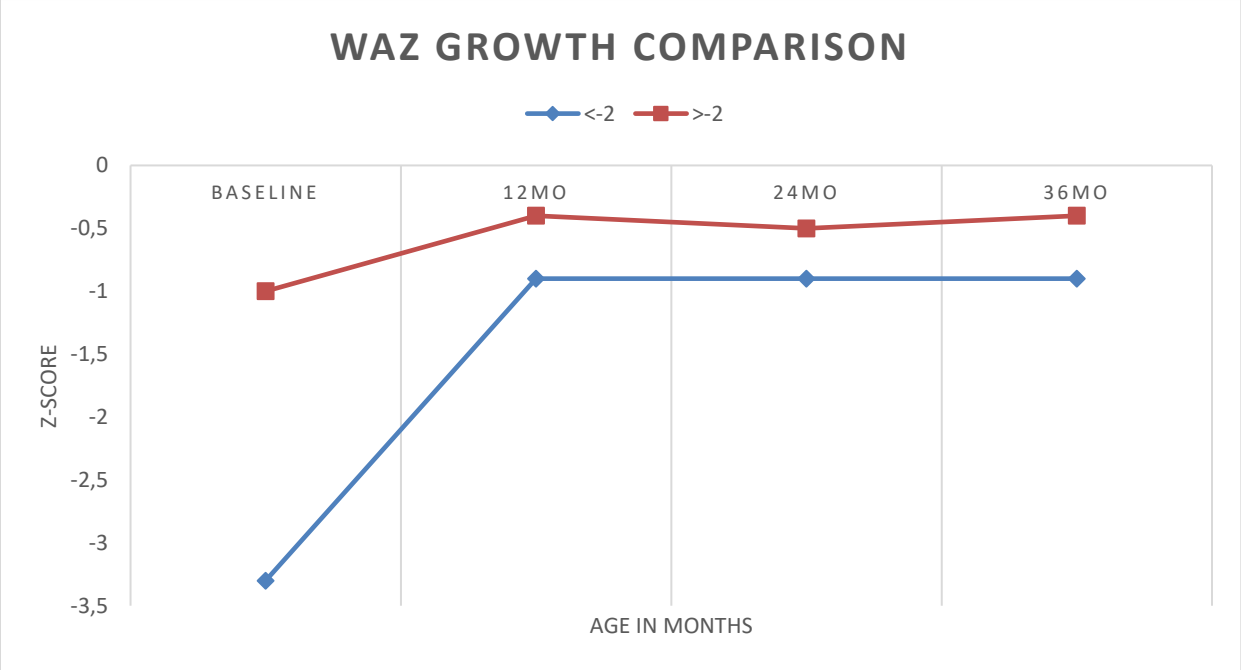

Figure 4.7 Growth Comparison of WAZ at ART Initiation and at 12, 24 and 36 months in those UWA and those Normal Weight for Age.

4.2.2 Height for Age

The majority of children were stunted (62%) at the time of initiating ART. There was an increase in HAZ, although at a more gradual rate when compared to WAZ. There was a steady improvement in the median Z-scores done pre-treatment and at 12, 24 and 36 months (see Table 4.4 and Figure 4.8 and 4.9). HAZ increased more rapidly in the first 12 months then plateaued thereafter as occurred with changes in WAZ.

At initiation of ART, children initiated between 2004 and 2007 were more likely to be stunted than those initiated between 2008 and 2010 with a median of -2.8 (IQR: -3.8 to -1.6) and -2.0 (IQR: -3.0 to- 1.3) respectively, p=0.0041. The more severely stunted children showed a faster recovery in the first 12 months, but after follow-up over three years, their HAZ increase slowed down. The difference in HAZ at three years was not more pronounced than that of WAZ and like WAZ remained significantly different after three years for children starting with stunting (p=0.009). Gender at initiation did not show a significant difference in terms of improvement in heights, but in terms of age at initiation there were important differences. Contrary to WAZ where the youngest patients had the lowest Z-cores, when it came to HAZ at initiation, the youngest patients had better Z-scores than the older patients. Although, population norms were not reached, WAZ reached closer to population norms when compared to HAZ as shown be median -0.5 (IQR: -1.1 to -0.02) and -1.0 (IQR: -1.7 to -0.1) respectively.

Table 4.4: Growth comparison of HAZ at ART initiation and at 12, 24 and 36 months after ART Initiation

	Baseline	HAZ at 12months	HAZ at 24months	HAZ at 36months
All Patients N=292	-2.4 (-3.6 to -1.4)	-1.7 (-2.7 to -0.7)	-1.4 (-2.2 to -0.6)	-1.2 (-1.9 to -0.4)
Males	-2.5 (-3.7 to -1.4)	-1.7 (-2.7 to -0.8)	-1.4 (-2.1 to 0.5)	-1.1 (-1.9 to -0.3)
Females	-2.4(-3.6 to -1.5)	-1.6(-2.7 to- 0.5)	-1.4 (-2.3 to 0.6)	-1.3 (-2.2 to -0.5)
P value	0.82	0.59	0.80	0.12
Initiation of ART in 2004-2007	-2.8 (-3.8 to -1.6)	-1.5 (-2.7 to -0.5)	-1.3 (-1.9 to -0.4)	-1.1 (-1.9 to -0.3)
Initiation of ART in 2008- 2010	-2.0 (-3.0 to -1.3)	-1.8 (-2.6 to -0.9)	-1.6 (-2.4 to -0.8)	-1.5 (-2.1 to-3.9)
P value	0.0041	0.46	0.060	0.01
Age category at initiation				
0-6 months	-1.6 (-2.9 to -0.9)	-1.4 (-2.1 to -0.7)	-1.3 (-2.2 to -0.3)	-1.6 (-2.2 to -0.4)
6-12months	-2.4 (-3.5 to -1.5)	-1.9 (-3.1 to -0.9)	-1.5 (-2.9 to -0.6)	-1.3 (-2.2 to -0.5)
12-24months	-3.0 (-4.0 to-2.2)	-1.8 (-2.8 to -0.8)	-1.5 (-2.4 to -0.8)	-1.3 (-1.9 to -0.8)
24-36months	-2.2 (-3.1 to -1.3)	-1.6 (-2.6 to -0.6)	-1.1 (-1.8 to -0.4)	-1.0 (-1.7 to -0.1)
P value	0.0006	0.23	0.10	0.021
<-2 Z score	-3.2 (-4.2 to -2.5)	-1.9 (-2.8 to -1.1)	-1.5 (-2.3 to -3.9	-1.4 (-0.8 to -4.3)
>-2 Z score	-1.1 (-1.5 to -0.4)	-1.2 (-1.8 to -0.1)	-0.9 (-1.7 to -0.0)	-0.9 (-1.7 to -0.0)
P-value	<0.0001	<0.0001	<0.0001	0.0009

Table 4.4: Medians are listed with IQR= Inter-quartile range

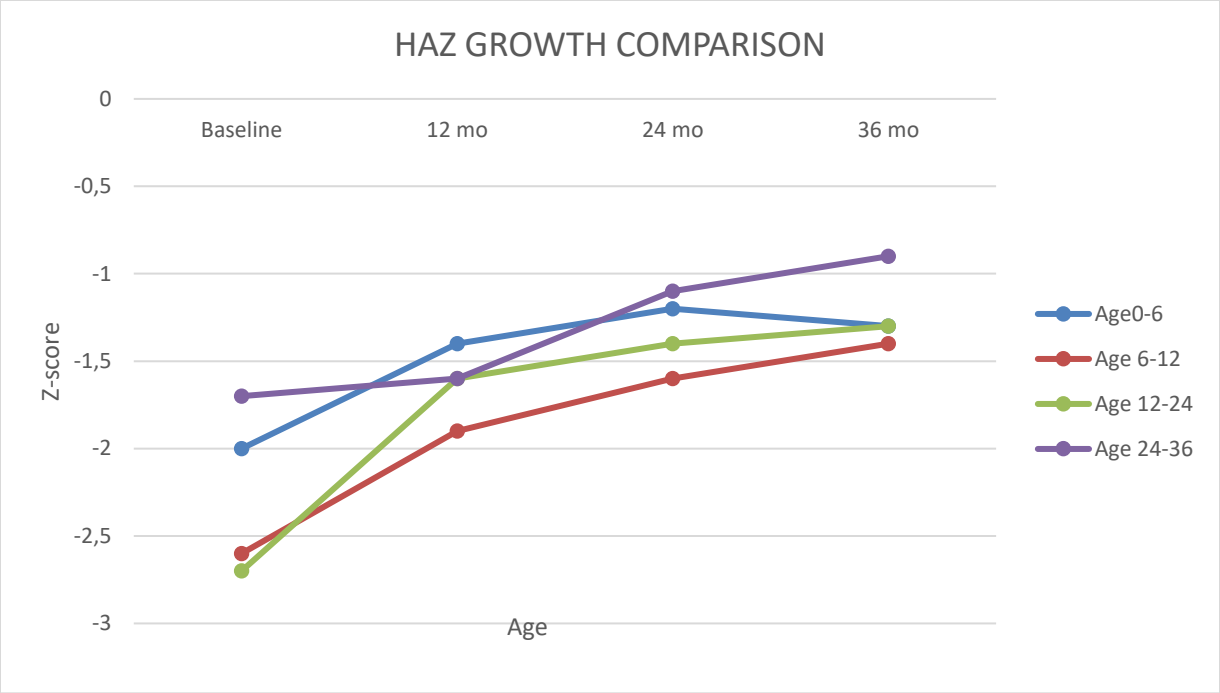

Figure 4.8 Growth Comparison of HAZ at ART initiation and at 12, 24 and 36 months.

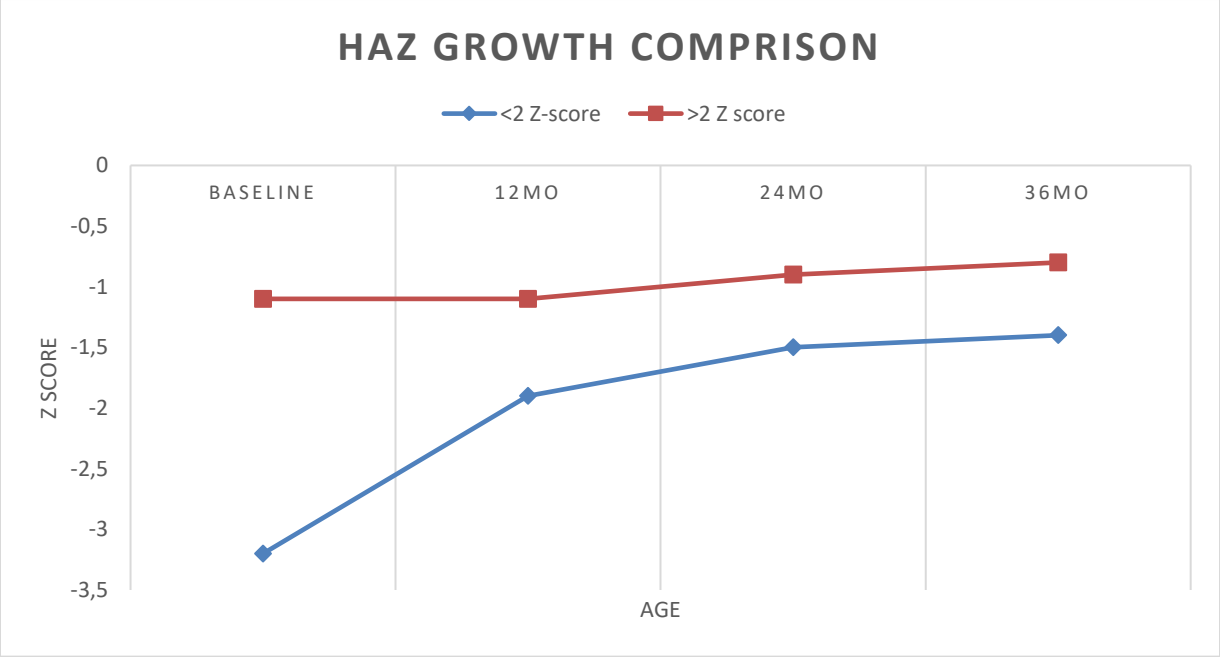

Figure 4.9 Growth Comparison of HAZ at ART initiation and at 12,24 and 36 months.

4.2.3 Weight-for-height

Twenty five percent of children were wasted at the start of ART, which was less common than stunting (62%) and UWA (55%) (Table 4.1). Three years after starting ART most of the children in our study population had reached the median WHZ score for age.

There was no significant difference in WHZ between the children initiated on ART in the period 2004 -2007 and those initiated between 2008 and 2010, (p=0.23). WHZ increased steadily on ART initiation and also plateaued after one year on ART. There was also no significant difference with increase in WHZ in terms of gender at any time period after ART initiation.

Children who were wasted (WHZ<-2) had a faster increase in WHZ in the first 12 months post ART initiation compared to those who were not wasted: They started at -3.1 (IQR: -4.3 to -2.6) and -0.4 (IQR: -1.1 to 0.5) and increased to 0.2 (IQR: -0.9 to 0.9) and 0.3 (IQR: -0.6 to 1.3) respectively.

As with WAZ, children less than 12 months of age pre-treatment had a lower WHZ when compared to those older than 12 months. This indicates that younger children were sicker than older children when initiating ART. Wasting recovered completely after a year on ART and after three years of follow-up there was no difference in the prevalence of wasting between the different age groups.

Table 4.5 Median (IQR) WHZ at Baseline, 12 months, 24 months and 36 months after ART initiation:

	Baseline	WHZ at 12 months	WHZ at 24 months	WHZ at 36 months
All Patients N=292	-0.9 (-2.0 to 0.2)	0.3 (-0.7 to 1.14)	0.2 (-0.7 to 0.9)	0.0 (-0.7 to 0.7)
Males	-0.9 (-2.1 to 0.3)	0.4 (-0.6 to 1.3)	0.2 (-0.6 to 1.0)	-0.0 (-0.8 to 0.6)
Females	-0.9 (-2.0 to 0.0)	0.1 (-0.8 to 0.9)	0.1 (-0.7 to 0.9)	0.1 (-0.8 to 0.5)
P-value	0.89	0.13	0.51	0.19
Initiation of ART in 2004-2007	-0.8 (-1.7 to 0.1)	0.4 (-0.7 to 1.2)	0.2 (-0.6 to 0.9)	-0.1 (0.8 to 0.5)
Initiation of ART in 2008- 2010	-1.1 (-2.5 to 0.3)	0.3 (-0.6 to 1.1)	0.2 (-0.6 to 0.9)	0.2 (-0.6 to 0.8)
P-value	0.23	0.74	0.77	0.23
Age category at initiation				
0-6 months	-1.3 (-2.5 to -2.1)	0.1 (-0.9 to 0.860	0.1 (-0.7 to 0.6)	0.0 (-0.8 to 0.6)
6-12months	-1.5 (-3.0 to -0.3)	0.2 (-0.9 to 1.1)	0.2 (-0.8 to 1.0)	0.1 (0.8 to 0.7)
12-24months	-0.9 (-1.8 to -0.1)	0.2 (-0.6 to 1.2)	0.2 (-0.7 to 1.0)	0.0 (-0.6 to 0.9)
24-36months	-0.1 (-1.1 to 0.7)	0.8 (-0.2 to 1.4)	0.2 (-0.4 to 0.9)	*
P-value	<0.0001	0.084	0.93	0.81
<-2 Z score	-3.1 (-4.3 to -2.6)	0.2 (-0.9 to 0.9)	0.1 (-1.2 to 1.0)	0.0 (-0.8 to 0.5)
>-2 Z score	-0.4 (-1.1 to 0.5)	0.3 (-0.6 to 1.3)	0.2 (-0.5 to 0.9)	0.1 (-0.7 to 0.7)
P-value	<0.0001	0.22	0.44	0.88

Table 4.5: WHZ scores compare growth with regards to WHZ scores at ART initiation and at 12, 24 and 36months. * No WHZ were available for the children starting ART at 24-36 months of age as they were >5 years old 36 months later and therefore no values were generated. Medians are listed with IQR= Inter-quartile range.

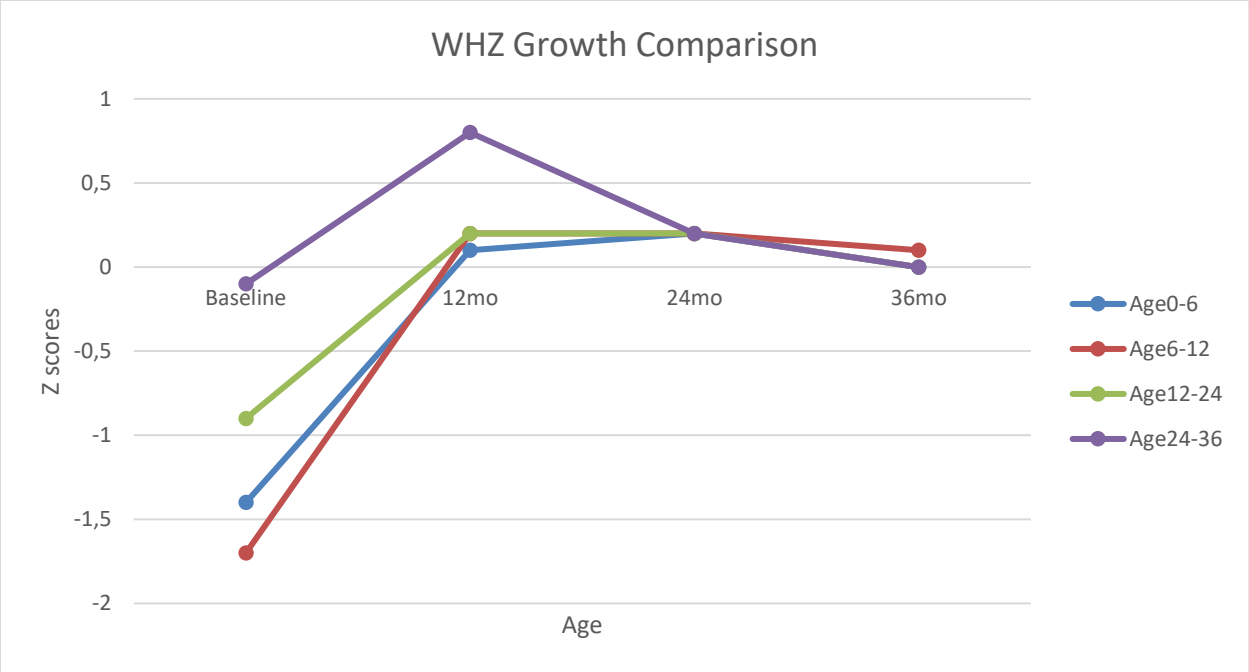

Figure 5.0 Growth Comparison of WHZ at ART initiation and at 12, 24 and 36 months.

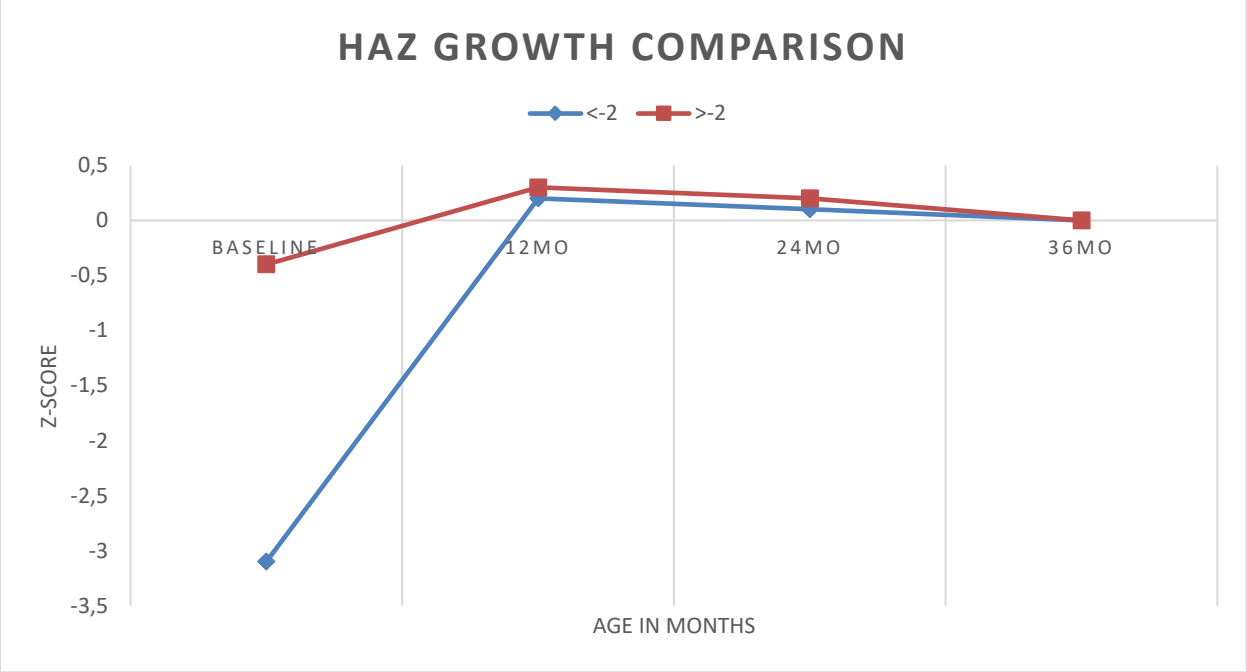

Figure 5.1 Growth Comparison of WHZ at ART initiation and at 12,24 and 36 months.

Chapter 5: Discussion

This study evaluated 292 HIV-infected children who were initiated on ART at Empilweni HIV Clinic at RMMCH between January 2004 and 31 August 2010. While younger children (0-12 months at initiation) had lower WAZ scores at initiation, older children (12-36 months at initiation) had lower HAZ scores at initiation. An important factor determining lower three years WAZ and HAZ scores was the starting Z-score of <-2, i.e. once a child's growth indicators were below -2 they were less likely to recover compared to children starting with better indicators.

Our findings showed that HAZ and WAZ showed a rapid increase in the first 12 months followed by a more stable growth thereafter for those initiated on ART: WAZ increased from -2.2 (IQR: -3.1 to -1.2) at initiation to just below -0.7 (IQR: -1.4 to -0.1) and HAZ increased from -2.4 (IQR: -3.6 to -1.4) to -1.7 (IQR: -2.7 to -0.7). WAZ scores at initiation of ART were lowest in younger children: -2.6 (IQR: -3.8 to -1.4) at 0-6 months and -2.7 (IQR: -4.3 to -1.9) at 6-12months. These results we found are in keeping with similar findings of a study done in another cohort in Johannesburg, where it was shown that in the first 12 months of ART treatment, children who were less than six months of age at ART initiation had experienced more rapid improvement in WAZ.[11] Similar results were also observed in a cohort study in Lilongwe, Malawi in which growth response in HIV-infected children starting ART was studied: the results of this study demonstrated an improvement in growth that occurred after starting ART: median (IQR) WAZ and HAZ increased from -2.1 (IQR: -2.7 to -1.3) and -2.6(IQR: -3.6 to -1.8) to -1.4 (IQR: -2.1 to 0.8) and -1.8(IQR: -2.4 to -1.1) at 24 months respectively ($p<0.001$).[8]

A different study showed contrary results to the above of a reversed trend of WAZ and WHZ from 2 years onwards, were as the initial analysis of 18000 HIV children in 12 ART programs had revealed an initial improvement in the first year of ART.[4] We also found that Z scores at initiation were crucial in predicting growth response, the more severely underweight children showed a more rapid catch-up growth on ART, but did not necessarily reach the same weight as children who had started out with higher values. In our study, having a low Z-score of <-2 was even found to be most important predictor for growth response when compared to age. This finding was also a similar finding in the Lilongwe, Malawi study[8]. It is important to asses if height increases beyond 36 months in our population will eventually reach the population norm.

Another main finding of our study at RMMCH was that more children were stunted (62%) than underweight (55%) or wasted (25%). Similar results were also observed in a cohort study in Lilongwe, Malawi in which growth response in HIV-infected children starting ART was studied: the results of this study showed that more than half the children were UWA and that two-thirds were stunted when starting therapy, fulfilling WHO clinical stage 3 or 4.[8] Similar findings were also documented in a cohort of 124 HIV-infected Ugandan children who were enrolled and initiated on HAART, their results showed that stunting (HAZ -2.0 (IQR -2.9-1.2)) was more prominent than wasting (WHZ -1.2 (IQR -2.1, -0.5)) at baseline.[12] It is of significance that the majority of HIV-infected children were stunted in our study at initiation of ART, as stunting is an indicator of chronicity. [12, 4] Of note, stunting was more prominent in older than in younger children. This finding may be explained by the fact that stunting as a measure of chronicity would be more common in HIV infected children who only access treatment after infancy. In Sub-Saharan Africa,

HIV-infected children have been noted not only to be stunted, but to have overall growth retardation early in life: effects on length for age and weight for age by age 3 months compared with values for seroverters were reported in a South African urban cohort.[19]

We also considered that the timing of HIV infection or transmission would also play a role in the final anthropometry as it is well known that intrauterine infected infants may be more growth delayed than postnatally infected infants or infants infected during breastfeeding. We however had no data regarding a birth HIV PCR, this may be a possible reason for the difference in the initiation groups. A study in South Africa that studied post neonatal deaths under one year of age found peak mortality to be at two to three months with intrauterine and intrapartum infection being speculated to have contributed to this peak.[20] This peak was also found to be an indicator of paediatric AIDS in a population with high HIV prevalence.[20] Another study showed that children infected with HIV perinatally had a high risk of dying than those infected from breastmilk.[21]

Another main finding of our study was that, age at initiation of ART significantly influenced the amount of growth recovery: lower WAZ were noted at initiation (ranging from -2.7 to -1.4 ($p<0.001$) from youngest to oldest children) and HAZ starting values (ranging from -3.0 to -1.6; $p=0.0006$), but much improvement was noted after initiation of ART with median ranges from WAZ: -0.8 to -0.6 ($p=0.37$) and HAZ: -1.3 to -1.0 after three years follow up. We also found that with regards to WAZ, age at initiation makes a significant difference in the amount of increase in Z-scores, ($p<0.001$). However, having a low WAZ is more common at a younger age median -2.6 (IQR: -3.8 to -1.4) than at the

end of 3 years, median -0.9 (IQR: -1.5 to -0.1). Thus, the final Z-scores was affected more by the baseline Z-scores and not as much by the age. Some studies in African children have also described growth benefits of early age at ART initiation.[22,23] One of these, is a study in Kenya amongst HIV-infected children initiated on HAART showed that 12 months post-HAART, children below three years had higher increases in WAZ and WHZ following HAART when compared to those 6-10 years.[22] It was also noted that these younger children also had more rapid catch-up to the population average weight of their peers than older children.[22]

Although, the specific reasons for more rapid catch up growth where not examined, the findings of our study indicate that children who were UWA or stunted did not manage to reach normal growth after three years of follow-up. The question of whether HIV-infected children initiated on ART with severe growth restrictions ever reach catch-up growth entirely still remains unanswered by our findings. African studies previously done already mentioned above also show an increase in WAZ and HAZ, but without ever reaching normal values.[11,6] In contrast to this, a study involving American children who were not yet on ART, showed that a normal WAZ was reached after one year and normal HAZ was reached after two years of ART initiation.[24] Our findings were of the contrary in that even after three years of follow up, normal WAZ and HAZ were not attained. This study also included much older children, with ages ranging from 0.4-16,3 years as compared to our study were the ages ranged from 7-23 months and had better baseline characteristics as evidenced by median WAZ of -0.74, HAZ -1.22 when compared to ours of WAZ of -2.1 and HAZ of -2.3.[24] This has been found to be a normal

reaction to the correction of growth retarding disorders; catch-up growth has been shown to firstly affect weight and then height.[24]

A study in Johannesburg showed that catch-up growth with regards to weight was faster initially, but catch up growth in height was more constant and continued over the two year time period.[11] Our findings were also similar when we compared growth in weight and height continuing over a three year period to this study in Johannesburg. In our study, although an increase in height occurred, it however occurred at a more gradual rate when compared with weight as shown by the steady but sure improvement in the medians done pre-treatment at 12, 24 and 36 months. We also noted in our study that WAZ<-2 was more common in young children whereas stunting was more common in older children. Both baseline WAZ<-2 and HAZ<-2 have a lasting effect and both suggest that ART before the advent of UWA or stunting is critical. Three years after starting ART, most of our study population's WHZ had reached the mean Z-score for age where as WAZ and HAZ did not reach the population norm. Children, who started off with WAZ and HAZ less than 2, had catch-up growth ending closer to the population mean than children with less depressed growth pre-treatment.

We also looked at the differences in the WAZ, HAZ and WHZ with regards to gender as it has been reported to affect growth in the context of HIV treatment.[14]A study in a South African cohort showed that pre-randomization to receiving ART, WAZ for boys and girls increased rapidly and WAZ for boys was greater than that for girls, however no statistically significant sex differences where noted post randomization to receiving different ART regimens.[14] A different study of older children, reported higher rates of stunting in boys when compared to girls.[24] Our study found that there were no significant sex differences

noted when comparing WAZ, HAZ and WHZ at baseline and over the first three years of treatment. Less is known about these gender differences when it comes to disease progression and response to ART among children.[6] Further investigations regarding gender and the effect on growth in HIV-infected children on ART are warranted.

A limitation to the study is that growth failure has many causes, as mentioned previously, it can be caused by: environmental, endocrine factors and genetic factors.[3, 4] These factors were not accounted for in our study and could have been confounding factors in our results. Children with pathology in addition to HIV have not been excluded, but it is anticipated that the incidence of primary growth disorders would be low. We also did not investigate known potential pathways for growth differences, such as immune activation, gastrointestinal or neuroendocrine abnormalities or dietary practices.[11] We also think it is likely that diet or nutritional factors would vary between children initiating therapy at different ages and would significantly impact the results.

Another confounding factor to consider in this research is that children younger than six months of age were some of the more wasted, UWA and stunted and thus presenting earlier with poor growth and severely affected growth parameters when compared to older children. ART treatment guidelines changed over time, resulting in the likelihood that children initiated in the earlier years of the roll-out were more likely to have worse baseline characteristics than those in later years. If sicker patients are more likely to get lost, our study had an exclusion criterion for those children who were lost to follow-up. It has been previously revealed that mortality is high among patients who get lost to follow-up.[4] Abacavir use was initiated in 2010 in place of d4T and this could potentially have resulted in different growth changes.[17] We did not look for differences between patients on

different ART regimens. There also could have been differences between patients on efavirenz compared to those on lopinavir/ritonavir. We also did not compare the growth of our HIV-infected children to HIV-negative children and did not adjust our growth parameters to normal growth patterns for baseline characteristics. Enrollments weights were comparable with age and sex adjusted norms in a study looking at growth in HIV-infected children receiving ritonavir-containing ART, but subjects receiving ritonavir-containing ART were found to be significantly shorter (mean Z-scores, -0.57 [29th percentile(95% confidence interval:, -0.73 to -0.40]).[25] It would have been beneficial to look at head circumference in these children but we were unable to do this due to inadequate data capturing of head circumference.

Another limitation to the study is that children who died were excluded. These might have all been young and stunted, or older with TB, or those with poor adherence i.e. we speculate that they could have been some of the sickest children. The growth response of these children may well differ to the findings in the cohort that remained.

A limitation also considered was that there were no additional parameters done to evaluate for wasting like mid upper arm circumference or triceps skinfolds. A low WHZ predicts wasting if it is acute, if a patient is chronically ill and not thriving due to severe stunting, the WHZ will not plot low and will not necessarily exclude low weight. Also, there may not be severe wasting, but in the presence of stunting where the weight is just as affected as the height, the WHZ will plot better, even though weight is not normal. Unfortunately the details of the feeding method (breast- vs. replacement milk and weaning practices) were not available for analysis but could arguably have played a significant role.

Despite various limitations to our study, a strength to the study was that our results are consistent with observations mentioned in various studies discussed above. This study also has a three year length of follow-up which is in keeping with the length of studies discussed and also extending beyond. Documentation of measurements of weight, height and weight for height was also frequent, allowing for good interpretation of data.

Our study demonstrates that early initiation of ART in HIV-infected children results in an improvement in their overall growth and plays a crucial role in their growth recovery, especially if their they are UWA. Despite the challenges of initiating ART in HIV-infected infants in a developing and low-resourced country, the importance of initiating ART as soon as possible after birth cannot be overemphasized. The above results are further confirmed by results from the CHER study in which early initiation of ART led to 76% reduction in mortality and 75% reduction in HIV disease progression.[12] A study in a similar cohort in Johannesburg also supports the above evidence, this study showed that the initiation of ART before 6 months of age was associated with faster growth recovery in South African children who were perinatally infected with HIV.[10]Another study in Kenya showed that among 43 infants, 47% and 67% were reported to have achieved viral suppression after 6 months of HAART.[25] These results serve as a motivation to health care workers at Empilweni HIV Clinic and South Africa at large, to document the correct date of birth, regular and accurate measurements of heights and weights and to plot the correct Z-scores diligently. This will assist in better studies compared to the one we have done. These studies may further assist in refining guidelines regarding initiation of ART in children and improve their lives.

Conclusion

In this study, it was shown that initiation of ART has a positive effect on the over-all growth of HIV-infected children. The recovery of WAZ and WHZ is much faster than the recovery of HAZ, but a plateau in growth occurred for all these growth parameters. Similar to other studies, the improvement in height lagged behind weight and weight for height. Despite sustained growth response and catch up growth in children with advanced HIV disease treated with ART, normal weights and heights are not achieved in 3 years. In this study, with regard to the outcomes of WAZ, HAZ and WHZ at 36 months on treatment, age at initiation of ART was not an important factor in predicting recovery, but having a Z-score <-2 prior to starting ART was found to be critical. Regardless of age at initiation of ART, no difference was detected in WAZ by 36 months. However, unlike WHZ, neither WAZ nor HAZ recovered to normal when children of any age up to three started ART once growth had already faltered. ART should be initiated as early as possible to precede growth faltering.

Recommendations

- Early initiation of ART before growth falters is recommended, as having a Z-score <- 2 prior to starting ART was found to be associated with lack of recovery to normal of WAZ and HAZ after 3 years on ART .
- Further studies looking at the growth of infants initiated on ART soon after birth are recommended.

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EMPILWENI Treatment Clinic - Consent Version 3 June 2011

CONSENT FORM: USE OF CLINICAL INFORMATION

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

Dear Guardian and Patient,

You/your child are currently attending Rahima Moosa Mother and Child Hospital for treatment of problems you/your child are/is currently experiencing. The Hospital not only renders treatment but is also actively involved in conducting research aimed at improving the quality of care we deliver. From time to time such research involves the use of patient records from which information is extracted. The use of such information is subject to:1 Approval from the Committee for Research on Human Subjects (University of the Witwatersrand)2 Anonymity i.e. the identity of the patient from whose file information is extracted is never revealed to anyone but the researcher unless specific consent is obtained to do so. Whilst we are not currently involved in research that requires us to use any information now, this may change in the future when you are already discharged. We would like to obtain your consent to use information from your file for the purpose of research, subject to the aforementioned conditions. If you choose not to give consent, this will not compromise your treatment in any way. If at any time you choose to withdraw consent you are free to do so and will not be prejudiced in any way. Should you wish to contact us at any stage regarding this consent, contact Rahima Moosa Mother and Child Hospital, Empilweni Clinic at (011) 470 9421.

A.I.....hereby give consent for my/my child's records to be used as per the abovementioned conditions for the purposes of research:
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SIGNATURE:.....
DATE:.....WITNESS:.....
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GUARDIAN NAME and
RELATION:.....
SIGNATURE:.....
DATE:.....WITNESS:.....
..... DATE:.....

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R14/49 Dr Lethabo Machaba

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CLEARANCE CERTIFICATE NO. M130823

NAME: (Principal Investigator) Dr Lethabo Machaba

DEPARTMENT: Department of Paediatrics
Rahima Moosa Mother & Child Hospital

PROJECT TITLE: Antiretrovial Therapy in HIV Infected Children- A Secondary Analysis of Growth Parameters Associated with Age at Inititian

DATE CONSIDERED: 30/08/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr Karl G Technau

APPROVED BY:
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/08/2013

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ESRU
Empilweni Service and Research Unit
Rahima Moosa Mother and Child Hospital
JOHANNESBURG
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Dear Ms. L. Machaba,

Permission is granted for you to conduct the above study as indicated in your request:

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3. Strict confidentiality shall be observed at all times.
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ANTIRETROVIRAL THERAPY IN HIV INFECTED CHILDREN- A SECONDARY ANALYSIS OF GROWTH PARAMETERS ASSOCIATED WITH AGE AT INITIATION By Lethabo Machaba-Simelani Student No:7883319 SUPERVISORS: 1. Dr Technau: Empilweni Clinic - Rahima Moosa Hospital MBBCh, MSc(Med) 2. Dr Gill Sorour: MBBCh,FCPaed, MMed,A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirement for the degree of Master of Medicine in the Department of Paediatrics Johannesburg, 2018 I Declaration I, Lethabo Machaba-Simelani, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University. ……. 01…… ……..day of…… August 2018. II Dedication This work is dedicated to my family: the Machaba and Simelani family (my husband and two children). Thank you for being the pillars I can lean on. 'I look up to the mountain, from whence cometh my help?... My help cometh from the Lord' Psalm 121 v 1-2 III Presentations Arising from this Work Poster Presentation at the 19th International Workshop on HIV Observational Database. Catania, Sicily 26th-28th March 2015. Title of Presentation: Antiretroviral therapy in HIV-infected children- A secondary analysis of growth parameters associated with age at initiation. IV Abstract Introduction: Growth failure in HIV infected children is a significant identifiable complication of HIV and can present as stunting, weight loss and or severe acute malnutrition (SAM). A description of the response of growth to ART initiated in young children is presented. Methods: A secondary data analysis of a prospective cohort of 292 HIV-infected children less than 3 years of age initiated on ART at a Johannesburg HIV Clinic between January 2004 and 31 August 2010 was done. Comparison of growth parameters for the time points 12, 24 and 36 months after initiation of ART was done in relation to age, gender, year of initiation, underweight for age (UWA), stunting or wasting at ART initiation.. Results: At ART initiation, almost half the children were UWA (55%), 62% were stunted and 25% were classified as wasted The recovery of weight-for-age Z-score (WAZ) and weight-for-height Z-score (WHZ) was much faster than the recovery of height-for-age Z-score (HAZ), however, analysis of all growth parameters showed a plateau of growth recovery after 3 years of follow-up. Lower WAZ was noted at initiation when compared to HAZ. UWA was more common in young children whereas stunting was more common in older children. Improvement after 3 years of follow up was noted for both weight and

height but recovery of HAZ did not reach the population median as closely as WAZ did. Conclusion: ART has a positive effect on the over-all growth of HIV-infected children. Age at initiation affected growth recovery in that younger children who were more severely affected at initiation showed better growth recovery. Despite sustained growth response and catch up growth in HIV-infected children on ART, normal weights and heights were not achieved after 3 years. V Acknowledgements The Author would like to acknowledge with deep appreciation and gratitude, the invaluable work of the following people: My supervisor: Dr Karl-Gunter Technau. This study would not have been possible without you. Thank you for the guidance provided and the passion passed on towards research. My Co-supervisor: Dr Gill Sorour. The input you made to this work is highly appreciated. Special Thanks to Lukhanyo Nyati for all the contribution you made towards this project. The Executive team at Rahima Moosa Mother and Child Hospital, for approving the study: Prof Keith Bolton, Head of Paediatric Department. Annie Jordan, Project Manager and Gatekeeper at Empilweni Services and Research Unit. Dr Edward Hank, Clinical Manager and Superintendent. Special Thanks to Prof A Coovadia for always being a great leader and a figure of hope to registrars. This has encouraged me to not give up. Family: My husband: Mr Summer Simelani and daughters Nala an Naledi Simelani for the continuous encouragement to continue with the project. VI Table of Contents

Declaration……II
Dedication……III
Presentations……IV
Abstract……V
Acknowledgements……VI Table of Content……VII
Nomenclature……IX List of figures……X List of Tables……XI 1 Chapter 1: Introduction……1 1.1 The HIV pandemic in South Africa……1 1.2 Growth Failure in HIV-infected Children ..... 2 1.3 WHO description of Growth.....
2 1.4 Impact of Anti-retroviral therapy on Growth ..... 3 1.5 South African HIV Guidelines ..... 4 1.6 Importance of this study ..... 6 2 Chapter 2: Study Objectives ..... 7 2.1 Objectives .....
..... 7 2.2 Null Hypothesis .....
.. 7 3 Chapter 3: Methods .....
8 3.1 Study Design: .....
. 8 3.2 Study Population .....

8 3.3 Data
Domain: .....
.. 9 3.4 Statistical
Methods 10
3.5 Ethical
Considerations 11
3.6
Funding .....
..... 12 4 Chapter 4:
Results .....
13 4.1 Study population and baseline
Characteristics..... 13 VII 4.2 Growth
Response 14
4.2.1 Weight- for-Age.....21 4.2.2 Height
for Age..... 25
4.2.3 Weight-for-
height 28 5
Chapter 5:
Discussion..... 31
6 Conclusion.....38 7
Recommendations.....38 8
References .....
..... 40 9 Appendix 1- Data
Sheet.....43 10 Appendix 2-
Consent.....44 11 Appendix 3-
Clearance Certificate from WITS Research and Ethics Committee.....45 12.
Appendix 4 - Consent from Superintendent at Rahima Moosa
Hospital .....46 VIII AIDS ART CDC DOH HAZ HIV HRCS RMMCH WHO WAZ
WHZ UWA Nomenclature Acquired Immune Deficiency Syndrome Antiretroviral
Therapy Centers for Disease Control and Prevention, USA Department of Health
Height-for-age Z-score Human Immunodeficiency Virus Human Resource
Science Council Rahima Moosa Mother and Child Hospital (previously Coronation
Women and Child Hospital) World Health Organization Weight-for-age Z-score
Weight-for-Height Z-score Underweight for age IX List of Figures Figure 1.1:
HIV prevalence in South Africa 2012.....1 Figure 3.1:
Inclusion and exclusion criteria for study population at RMMCH..... 9
Figure 4.1: Overview of study
population ..... 14 Figure 4.2:
Number of children initiated yearly on ART at Empilweni HIV Clinic 15
Figure 4.3: Distribution of age of WAZ at baseline.....17
Figure 4.4: Distribution of age of HAZ at baseline.....17
Figure 4.5: Distribution of age of WHZ at baseline.....18
Figure 4.6: Growth Comparison of WAZ at ART Initiation.....24
Figure 4.7: Growth Comparison of WAZ at ART Initiation.....24
Figure 4.8 Growth Comparison of HAZ at ART Initiation.....27
Figure 4.9 Growth Comparison of HAZ at ART Initiation.....27
Figure 5.0 Growth Comparison of WHZ at ART Initiation.....30
Figure 5.1 Growth Comparison of WHZ at ART Initiation.....30
X List of Tables Table 4.1: Pre-Treatment Characteristics of Children initiatd on
ART at RMMCH ..... 19 Table 4.2: Pre-Treatment Characteristics of Children

initiated on ART at RMMCH…...20 Table 4.3: Median(IQR) WAZ at Baseline, 12months, 24months and 36 after ART Initiation .... 23 Table 4.4: Median(IQR) HAZ at Baseline, 12months, 24months and 36 after ART Initiation……....26 Table 4.5 Median(IQR) WhZ at Baseline, 12months, 24months and 36 after ART Initiation…….....29 XI Chapter 1: Introduction 1.1 The HIV pandemic in South Africa The Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) pandemic has had its greatest impact in Africa, with an estimated 7.1 million adults and children living with HIV at the end of 2016.1 In South African children, infection with HIV is still a great cause of morbidity and mortality with 320,000 children estimated to be living with HIV at the end of 2016. An estimated 1.7million children were also orphaned due to HIV by 2016.1 The numbers reported above have increased when compared to those released by Human Science Research Council (HSRC) in 2012, who reported an estimated 6.4 million people living with HIV in South Africa in 2012.2 Further results from this HSRC report also indicated that children contributed significantly to the South African overall burden of HIV (Figure 1).2 Figure 1.1: HIV prevalence in South Africa 2012 1.2 Growth Failure in HIV-infected Children Growth abnormalities are one of the biggest causes of morbidity in HIV-infected children.4 Growth failure can present as stunting, weight loss and or severe acute malnutrition with a poor response to nutritional rehabilitation.4 The mechanisms of growth failure in this group of children are complex and include genetic and environmental factors such as poor nutrition, low socioeconomic status and infection by different pathogens including perinatally acquired infections.4 Other factors that can contribute to this growth failure are changes in metabolic and endocrine function related to HIV infection.5 Many studies in Africa have demonstrated that poor growth is a sensitive indicator of HIV disease progression. 6 One such study done in Uganda, showed that HIV-infected children who had more severe disease: stage II, III, IV before initiation of treatment were 1.5 times more likely to become underweight (OR 1.51, CI 1.07-2.14).7 A study in Lilongwe, Malawi, demonstrated that both the baseline weight-for-age Z-score (WAZ) and the height-for- age Z-score (HAZ) were the most important determinants of growth trajectories of HIV- infected children on antiretroviral therapy (ART).8 1.3 WHO description of Growth The World Health Organisation (WHO) Multicentre Growth Reference Study was implemented between 1997 and 2003 with the purpose of designing a standard of growth for children. Deviations from this normal pattern of growth can thus be described as abnormal.9 The growth standards derived from this study have provided us with a tool that describes good physiological growth in children less than five years of age of all ethnicity, socio-economic status and feeding practices. To assess growth, the WHO has adopted the Z-score system as a means for analysis and presentation of anthropometric data. This system allows a child or group of children to be compared to a reference population. The Z-score system allows for the expression of the anthropometric value as a number of standard deviations (SD) or Z-scores below or above the reference mean or median, thus allowing for the following definitions of poor growth.9: ? Decreased HAZ (stunting): -2 SD below the mean (0). ? Decreased WAZ (underweight for age):

-2 SD below the mean (0). ? Decreased WHZ (wasting): -2 SD below the mean (0). ? Severe acute malnutrition (SAM): WHZ -3SD below the mean(0).9 Growth in HIV-infected children has long been regarded as being of great importance as displayed by the universal inclusion of growth abnormalities as a criterion for severe disease in both Centers for Disease Control and Prevention (CDC) and WHO classification systems. Several studies done in the United States of America on HIV- infected children have shown that normal WAZ was reached within a year of ART initiation, whilst HAZ normal parameters were attained within 2 years of ART initiation.10 1.4 Impact of Anti-retroviral Therapy on Growth It has been shown that access to antiretroviral therapy (ART) in low and middle-income countries increased from 400 000 in 2003 to 6.65 million in 2010 which resulted in a decreased number of people dying from AIDS.3 More updated South African statistics reported that there were 3.9 million people living with HIV and on treatment in 2016.1 The introduction of ART in developing countries has also played an important role in the improvement of not only growth, but also more importantly, in the survival of children infected with HIV. 10 One such improvement is specific to Sub-Saharan Africa, where recent studies have reported that, despite the high prevalence of growth failure in HIV- infected children, there is significant weight gain and increase in height that occurs after initiation of ART.11 Results from a study in Uganda showed that the mean increase in WAZ and HAZ in children initiated on ART was from -0.98(1.7SD) to +1.22(1.2SD) and – 1.99(1.7SD) to +0.76(2.4SD) respectively11. The Children with HIV Early Antiretroviral Therapy (CHER) trial also supports early initiation of ART. Their findings showed early ART reduced infant mortality by 76% and HIV progression by 75%.12 Despite the implementation of programs to improve access to ART, South Africa is still encountering vast challenges with the effect that the HIV pandemic is having on people's lives every day.3 The question often asked is: Does age at initiation of ART have a positive influence on growth? Several African studies mentioned above, have answered "yes" to this question as they have indicated that earlier age at initiation of treatment has a positive effect on growth. 7,8,10 However, ART-related improvements in WAZ have been shown to occur before improvements in HAZ. 7 The long-term consequences of HAZ (stunting) below normal levels remain unclear. Not much is also known about sex differences in growth response to ART in HIV-infected children.13 1.5 South African HIV Guidelines In 2004 South Africa formulated HIV treatment guidelines to ensure optimal therapy and good clinical outcomes. Part of guidelines also included follow-up visits during which weight, height and head circumference must be recorded and plotted on growth charts.13 4 In the 2004 guidelines first-line therapy included two Nucleoside Reverse Transcriptase Inhibitors (NRTI: stavudine [d4T] and Lamivudine [3TC]), together with either a Non- Nucleoside Reverse Transcriptase Inhibitor (NNRTI) in children three years or older or a Protease Inhibitor (PI) in children less than three years old.13 The criteria for starting ART included both medical and psychosocial criteria. Medical criteria included: modified WHO stage 3 or 4 disease; or children with CD4 percentage less than 20% in children under 18 months old; and CD4 less than 15% in children over 18months. The psychosocial criteria mainly included an identifiable and reliable adult able to administer ART and who has disclosed to another adult living in the same house.13 In 2008 the guidelines were further modified. All children with WHO stage 3 or 4 disease were to be started on treatment

irrespective of age. Immunological criteria for starting ART were age based: 1. Children less than 1 year: CD4 < 35 % 2. 1-5 years: CD4 < 20% 3. > 5 years: CD4 < 15%.14 The psychosocial criteria were similar to those in 2004 and the same drugs were used.14 Due to the side-effect profile of d4T, especially lipodystrophy and other mitochondrial side effects, abacavir (ABC) was introduced in place of d4T as first line therapy in 2010.15 Guidelines for the eligibility of ART were also further modified in 2010: all children less than one year of age qualified for ART, children between one and five years of age could receive ART if their CD4 was less than 750 absolute count or 25%; those greater than five years of age qualified for ART if CD4 was less than 350; WHO stage three or four 5 diseases was a criteria for all ages.15In 2013, new guidelines recommended that all children under five years of age qualified for treatment regardless of CD4 count.16 Children older than five years of age qualified if their CD4 was less than 350 or if they were WHO stage three or four.16 In September 2016, a Universal Test and Treat Strategy was implemented and recommended that all HIV-infected people be started on ART irrespective of clinical or immunological status. The changes in the guidelines over time would likely affect the baseline characteristics of children initiating ART and should therefore be taken into account when analyzing the growth response of children to ART initiation. The South African guidelines have also been noted to strive towards enabling earlier and earlier initiation of ART in HIV-infected children. 1.6 Importance of this study It is important that we know and are able to describe the changes in the following growth parameters in HIV-infected children following initiation of ART: WAZ, HAZ and WHZ. Another question that needs to be answered is how age at initiation and growth status at initiation of ART influences these growth parameters as treatment proceeds. The first years of life are important in providing a child with a good growth foundation and also in ensuring normal growth later in life. This study therefore also looks at the effect of a younger age at ART initiation on growth. Chapter 2: Study Objectives Objectives 1. Describe the change of WAZ, HAZ and WHZ between initiation and at 12, 24, and 36months post ART. 2. Describe the effects of age at initiation of ART: (stratified into four groups as less than 6 months, 6-12; 12-24 months and 24-36 months), on the growth change in objective 1. Null Hypothesis Age at initiation of ART does not affect the improvement in growth parameters in the first 3 years of treatment in HIV-infected Children. Chapter 3: Methods 3.1 Study Design: This study is a retrospective secondary analysis of a prospective cohort of HIV infected children attending Empilweni HIV Clinic, which is part of Rahima Moosa Mother and Child Hospital. 3.2 Study Population Empilweni Clinic has lived up to the meaning of its name: "where there is life". To date there have been more than 4000 children initiated on ART and an estimated 1600 children actively attending the clinic. All children at this site are HIV-infected and are managed in accordance with the South African HIV National guidelines. Enrolment of children onto ART at this site is in line with the national roll-out of ART which begun in 2004 and is still ongoing allowing a database of those initiated on ART to be established. De-identified data of patients from the beginning of 2004 until 31 August 2010, was extracted from this existing database and was used for this study. Patients lost to follow-up, transferred out or those who died were not included in this study as they did not meet the inclusion criteria. (See figure 3.1) Inclusion Criteria: ? Children enrolled from 2004-31 Aug 2010 ? Children must have initiated ART

between birth and 36months of age. ? Children must have had at least 3 years follow up at Empilweni HIV Clinic. ? Exclusion Criteria: Transfers in (started ART elsewhere) ? Children for whom the ART initiation date is unknown ? Death or loss to follow-up before completing 3 years of ART Figure 3.1: Inclusion and exclusion criteria for study population at RMMCH. 3.3 Data Domain: The following patient characteristics were extracted from the database created at Empilweni Clinic: 1. Age at ART initiation 2. Gender 3. WAZ (weight-for-age at baseline, 12, 24 and 36 months) 4. HAZ (height-for-age at baseline, 12, 24 and 36 months) 5. WHZ (weight-for-height at baseline, 12, 24 and 36 months) Baseline values were taken as the measure closest to the date of ART initiation from 2 months before to one week after initiation of ART. Values for 12, 24 and 36 months were taken from a window of 2 months around those time points for each patient to allow consistency. If there was more than 1 value in a window, the one closest to the 12, 24 and 36 month time points was chosen. Z-scores were calculated for weight-for-age, height-for-age and weight-for-height in accordance with the World Health Organization growth standard from 2007 using SAS version 9.3, (Cary, North Carolina, USA) Apart from actual values the following categories were created: ? Decreased HAZ (stunting): -2SD below the mean (0) ? Decreased WAZ (underweight): -2SD below the mean (0) ? Decreased WHZ (wasting): -2SD below the mean(0).9 Data cleaning was done for variables that were outliers to the normal distribution of variables. The variables concerned were re-checked by pulling out master files from records, verifying recorded growth parameters and correcting errors. These were largely data capturing errors. This validation was made possible as each anthropometric measurement was recorded for every child with each visit and questionable parameters were excluded or corrected. 3.4 Statistical Methods The results captured were entered into a Microsoft Office Excel database. A separate database was extracted from the main database which did not contain patient identifiers other than a study number (See Appendix 1). This data gathered was analysed using Epi Info 7 (7.1.4) and SAS version 9.3 (Cary, North Carolina, USA). 10 Basic statistical methods were used to analyze the data. Continuous variables were documented as median and inter-quartile range. Categorical variables were presented as frequencies and proportions. The above mentioned generated Z-scores taken for the 12, 24 and 36 months of age at initiation groups were compared using the Chi-Square test for categorical variables. The continuous parametric variables were compared using ANOVA and t-tests for the 12, 24 and 36 months of age at initiation groups. Those variables which were non-parametric were compared using the Wilcoxon signed rank test. All statistical comparisons were assessed for statistical significance at the alpha =0.05 level. 3.5 Ethical Considerations Empilweni Clinic has an existing ethics approval for the analysis of routine data and all patients were invited to sign a consent form for the use of their data (Appendix 2). Patients/caregivers who opted not to have their data included were excluded from the analysis. Parents had to sign, as children were minors. Only de-identified data was extracted from the existing database at Empilweni HIV Clinic into a Microsoft Excel sheet and permission to use the data was obtained from the clinic's Gate-Keeper. Written permission was obtained from the Medical Superintendent at Rahima Moosa Hospital (Appendix 4). Permission to proceed with this study was approved by the Post Graduate Committee of the University of the Witwatersrand. The same proposal was also submitted to the Human Research Ethics Committee of the

University of Witwatersrand who granted permission for this data review to be done (Appendix 3). 11 3.6 Funding This project needed minimum funds to cover printing costs and transportation to RMMCH. This was self-funded. Chapter 4: Results 4.1 Study Population and Baseline Characteristics The selection of children and how they played a role in the analysis is demonstrated in Figure 4.1. From the start of Empilweni HIV Clinic in 2004 there were a total of 3491 children started on ART between January 2004 and 31 August 2010. Of these 3491 children, 292 met inclusion criteria for this study. To perform the growth analysis, these children were divided into 4 groups by age at initiation of ART: ? <6 months (n=63), ? 6-12 months (n=69), ? 12-24 months (n=92), ? 24-36 months (n=68). No of children-initiated on ART at Empilweni Clinic from 2004-31 August 2010 (n= 3491) No of children excluded (n=3198) Did not start ART or started elsewhere: n=1413 Did not start between age 0 and 36 months: N=1172 Did not follow-up to 36 months: N=480 No consent or enrolled in other study, N=134 No of children initiated at RMMCH between birth and 36 months at RMMCH with 3 years follow up (n= 292) No of Children included in study (n=292) No of Children between 0-6months (n=63) No of children between 6-12months (n=69) No of children between 12 and 24months (n=92) No of children between 24- 36 months (n=68) Figure 4.1 Overview of study population. The population reviewed was HIV positive children at Empilweni clinic at RMMCH enrolled from January 2004 until 31 August 2010. These children were all initiated on ART between birth and 36 months of age, with age cut offs being based on age of initiation of ART as stipulated above. The distribution of ART initiation year for the children included in this study is shown in Figure 4.2. It was noted that the year 2004 had the lowest percentage of children initiated on ART (5%), but the number of children initiated on ART increased thereafter with 2007 having the highest percentage of 20 %. Figure 4.2: Number of children initiated yearly on ART at Empilweni HIV Clinic: Number of children's data evaluated between 2004 and 2010 at Empilweni HIV Clinic. The characteristics of the 292 HIV-infected children who were initiated on ART from 2004 until 2010 are shown in Table 4.1. Almost half (58%) of the HIV-infected children in the study were initiated on ART between 2004 and 2007. At initiation, the median age of the children was 13.8 months (Interquartile range [IQR]: 7 to 23 months). A further illustration of the age distribution is shown in Figures 4.3,4.4 and 4.5 in accordance to WAZ, HAZ and WHZ respectively. Close to half the HIV-infected children where underweight for age (55%), 62% were stunted and 25% were wasted. When looking at year of initiation, it was noted that younger HIV-infected children (0- 12months) were more likely to be enrolled in the later years (2008-2010) and more older children (>12months) earlier (refer to table 4.2). Further analysis showed that underweight at initiation was equally common throughout the two eras (p=0.91). Stunting at ART initiation was significantly more common in the earlier era (2004 – 2007) p=0.0009, low WHZ was much less frequent than underweight and stunting and almost similar between the eras (20% in early era and 31% in later era, p= 0.004). Figure 4.3 Distribution of age of WAZ at ART initiation Figure 4.4 Distribution of age of HAZ at ART initiation Figure 4.5 Distribution of age of WHZ at ART initiation Table 4.1: The pre-treatment characteristics of children initiated on ART at RMMCH. Baseline Characteristics: N (%) All children 292 Median age in months (IQR) 13.8 (7,23) 0-6 months 63 (22) 6-12months 69 (24) 12-24months 92 (32) 24-36months 68 (23) Female sex 141 (48)

Underweight: WAZ < -2 135(55)* Stunted: HAZ< -2 152 (62)* Wasted: HAZ< -2 62 (25)* Median WAZ (IQR) -2.1(-3.3,-1.2) Median HAZ (IQR) -2.4(-3.6,-1.5) Median WHZ (IQR) -0.1(-2.1,0.2) Table 4.1: All statistics are given as N (%) unless specified otherwise. * Denominator for baseline WAZ, HAZ and WHZ values was 246.WAZ= weight-for-age Z-scores, HAZ= height-for-age Z-scores, WHZ= weight-for-height Z-scores, IQR = Inter-quartile range. Table 4.2: The pre-treatment characteristics of children initiated on ART at RMMCH. Total no of children pre- treatment. 0 – 6 months 6-12 months 12- 24 months 24 – 36 months P value All children, N(row %): 292 63 (22) 69 (24) 92 (32) 68 (23) 0.81 Female 141 (48) 31 (49) 36 (52) 44(47) 30 (44) 0.82 2004 – 2007, N (%) 169 (58) 31 (49) 30 (43) 67 (40) 41 (60) 0.0009 2008 – 2010, N (%) 123 (42) 32 (51) 39 (57) 25(27) 27 (40) WAZ<-2 Z-score, N (%) 135 (55)* 35(67.3) 38 (67) 46 (59) 16 (23) <0.0001 HAZ<-2 Z-score,N (%) 153 (62)* 23 (44) 35(63) 62(41) 33 (55) <0.0004 WHZ<-2 Z-score,N %) 62 (25)* 20 (38) 22(39) 15 (19) 5 (9) <0.0001 Table 4.2 shows the pre-treatment characteristics of children who were initiated on ART at RMMCH, Empilweni HIV Clinic. * The denominator for WAZ, HAZ and WHZ baseline values was 246. All percentages are column percentages unless otherwise indicated. WAZ= weight-for-age Z-scores, HAZ= height-for-age Z-scores, WHZ= weight-for-height Z-scores 4.2 Growth Response 4.2.1 Weight-for-Age In terms of WAZ, there was a rapid increase in Z-scores in the first 12 months post- initiation of ART, followed by a more stable growth recovery thereafter. The median weight Z-scores increased from -2.2 (IQR: -3.1 to -1.2) at initiation to just below -0.7 (IQR: -1.4 to -0.1) at 12 months (Table 4.3). The subsequent plateau in growth is demonstrated by a fairly static median Z-scores at 24 months and 36 months, of -0.7 (IQR: -1.3 to -0.1) and -0.8(IQR: -1.4 to -0.1) respectively. When stratified by age at initiation this difference in growth is noted mainly at initiation ($p<0.0001$) but no longer noted by 12 months ($p=0.282$), 24 months ($p=0.38$) and 36 months ($p=0.37$). Children who were underweight (WAZ < -2) and of normal weight (WAZ>-2) at ART initiation demonstrated an increase in WAZ in the first year of life, with a more rapid increase in weight for those UWA (Table 4.3 and Figure 4.7). The group with a WAZ- score> -2 at initiation, who also are the older children, had a smaller increase in z scores when compared to the UWA, as they started off at a better Z-score of -1.1 (IQR-1.5 to - 0.3). There was a noticeable significant difference between the two groups (WAZ > -2 and WAZ < -2) at initiation of ART with regards to Z-scores, $p<0.0001$, with a median Z- score of -1.1 (IQR -1.5 to -0.3) in children starting with WAZ > -2, compared to -3.0(IQR - 3.9 to -2.4) in children starting with WAZ< -2. Figure 4.7 demonstrates how both groups end up on fairly similar Z-scores after 3 years of follow-up having started far apart at initiation of ART. When children were analyzed in terms of their age, children in the age categories <6 months and 6-12 months at ART initiation started off with worse growth parameters for 21 WAZ: -2.6(IQR: -3.8 to -1.4) and -2.7(IQR: -4.3 to -1.9) compared to children above 12 months, WAZ: -2.2(IQR: -2.9 to -1.4) and -1.4 (IQR: -2.0 to 0.4) (P< 0.0001), but also had a greater increase in WAZ within the first years. By 36 months, children aged <6months and 6-12 months at initiation had gained 1.8 (IQR:0.8 to 2.9) and 1.8 (IQR: 0.8 – 3.1) respectively whilst children aged 24-36 months at initiation only gained 0.6(IQR: 0.0 to1.3). The findings of this study, therefore, indicate that with regards to WAZ, age at initiation is significant in terms of the difference at baseline. Having a low Z score is more

common at a younger age. The final z score after three years of ART was not found to be significantly different when stratified by the age at initiation but remained different when stratifying by the Z-Score at initiation being <-2 SD vs > -2.0 SD (p<0.0001). There was no significant difference in weight at initiation or after three years of ART when stratifying by gender (p > 0.05). Table 4.3 Median (IQR) WAZ at Baseline, 12 months, 24 months and 36 months after ART initiation: N= 292 Baseline WAZ at 12months WAZ at 24months WAZ at 36months All Patients N= 292 -2.2 (-3.1 to -1.2) -0.7 (-1.4 to -0.1) -0.7 (-1.3 to -0.1) -0.8 (- 1.4 to – 0.1) Males -2.2(-3.3 to -1.2) -0.7 (-1.3 to 0.1) -0.6 (-1.2 to 0.1) -0.7 (-1.3 to -0.1) Females -2.2(-3.1 to -1.1) -0.7(-1.6 to -0.1) -0.8 (-1.3 to -0.2) -0.8(-1.5 to 0.1) P -value 1 0.95 0.31 0.39 0.35 Initiation of ART in 2004- 2007 -2.1 (-3.2 to -1.2) -0.7 (-1.4 to 0.1) -0.6 (-1.2 to -0.1) -0.8(-1.3 to -0.1) Initiation of ART in 2008 - 2010 -2.2 (-3.1 to -1.1) -0.7 (-1.4 to 0) -0.8(-1.5 to -0.2) -0,7(-1.5 to -0.2) P -value 2 0.44 0.89 0.28 0.55 Age category at initiation: 0 – 6 months -2.6 (-3.8 to -1.4) - 0.6 (-1.3 to 0) -0.9 (-1.3 to 0.4) -0.9 (-1.5 to -0.1) 6- 12months -2.7 (-4.3 to -1.9) -0.7 (-1.6 to -0.2) -0.7 (-1.3 to -0.2) -0.8 (-1.2 to -0.2) 12- 24months -2.2(-2.9 to -1.4) -0.9(-1.5 to -0.2) -0.7 (-1.5 to -0.2) -0.7 (-1.6 to -0.3) 24 – 36 months -1.4(-2.1 to -0.4) -0.5(-1.3 to 0.2) -0.6(-0.9 to 0.1) -0.5(-1.1 to -0.02) P value <0.0001 0.28 0.38 0.37 <-2 Z score -3.0 (-3.9 to -2.4) -0.9 (-1.8 to 0.3) -0.9 (-1.5 to -0.3) -1.0 (-1.6 to-0.4) >-2 Z score -1.1 (-1.5 to -0.3) -0.4 (-1.0 to 0.5) -0.5 (-0.9 to 0.3) -0.4 (-1.1 to O.1) P-value <0.0001 <0.0001 0.0003 <0.0001 Table 4.3: Growth comparison of WAZ at ART initiation and at 12, 24 and 36 months WAZ GROWTH COMPARISON 0 BASELINE 12MO 24MO 36MO -0.5 -1 Z-SCORE Age0-6 -1.5 Age6-12 Age12-24 -2 Age24-36 -2.5 -3 AGE IN MONTHS Figure 4.6 Growth Comparison of WAZ at ART Initiation and at 12, 24 and 36 months. WA Z G R O W T H C O M PA R I S O N <-2 >-2 0 BASELINE 12MO 24MO 36MO -0.5 -1 Z-SCORE -1.5 -2 -2.5 -3 -3.5 AGE IN MONTHS Figure 4.7 Growth Comparison of WAZ at ART Initiation and at 12, 24 and 36 months in those UWA and those Normal Weight for Age. 4.2 .2 Height for Age The majority of children were stunted (62%) at the time of initiating ART. There was an increase in HAZ, although at a more gradual rate when compared to WAZ. There was a steady improvement in the median z scores done pre-treatment and at 12, 24 and 36 months (see Table 4.4 and Figure 4.8 and 4.9). HAZ increased more rapidly in the first 12 months then plateaued thereafter as occurred with changes in WAZ. At initiation of ART, children initiated between 2004 and 2007 were more likely to be stunted than those initiated between 2008 and 2010 with a median of -2.8(IQR -3.8 to - 1.6) and -2.0(IQR: -3.0 to-1.3) respectively, p=0.0041. The more severely stunted children showed a faster recovery in the first 12 months, but after follow-up over 3years, their HAZ increase slowed down. The difference in HAZ at three years was not more pronounced than that of WAZ and like WAZ remained significantly different after 3 years for children starting with stunting (p= 0.009). Gender at initiation did not show a significant difference in terms of improvement in heights, but in terms of age at initiation there were important differences. Contrary to WAZ where the youngest patients had the lowest z scores, when it came to HAZ at initiation, the youngest patients had better z scores than the older patients. Although, population norms were not reached, WAZ reached closer to population norms when compared to HAZ as shown be median -0.5(-1.1 to -0.02) and -1.0(-1.7 t0 -0.1) respectively. Table 4.4: Growth comparison of HAZ at ART

initiation and at 12, 24 and 36 months after ART Initiation N= 292 Baseline (0) HAZ at 12months HAZ at 24months HAZ at 36months All Patients N(292) -2.4 (-3.6 to -1.4) -1.7(-2.7 to -0.7) -1.4(-2.2 to -0.6) -1.2(-1.9 to -0.4) Gender: Males -2.5(-3.7 to -1.4) -1.7 (-2.7 to -0.8) -1.4 (-2.1 to 0.5) -1.1 (-1.9 to -0.3) Females -2.4(-3.6 to -1.5) -1.6(-2.7 to- 0.5) -1.4 (-2.3 to 0.6) -1.3 (-2.2 to -0.5) P value 0.82 0.59 0.80 0.12 Initiation of ART in 2004- 2007 -2.8(-3.8 to -1.6) -1.5(-2.7 to -0.5) -1.3(-1.9 to -0.4) -1.1(-1.9 to -0.3) Initiation of ART in 2008- 2010 -2.0(-3.0 to -1.3) -1.8(-2.6 to -0.9) -1.6(-2.4 to -0.8) -1.5(-2.1 to-3.9) P value 0.0041 0.46 0.060 0.01 Age category at initiation 0-6 months -1.6(-2.9 to -0.9) -1.4(-2.1 to -0.7) -1.3(-2.2 to -0.3) -1. 6(-2.2 to -0.4) 6-12months -2.4(-3.5 to -1.5) -1.9(-3.1 to -0.9) -1.5(-2.9 to -0.6) -1.3(-2.2 to -0.5) 12-24months -3.0(-4.0 to-2.2) -1.8(-2.8 to -0.8) -1.5(-2.4 to -0.8) -1.3(-1.9 to -0.8) 24-36months -2.2(-3.1 to -1.3) -1.6(-2.6 to -0.6) -1.1(-1.8 to -0.4) -1.0(-1.7 to -0.1) P value 0.0006 0.23 0.10 0.021 <-2 Z score -3.2(-4.2 to -2.5) -1.9(-2.8 to -1.1) -1.5(-2.3 to -3.9 -1.4(-0.8 to -4.3) >-2 Z score -1.1(-1.5 to -0.4) -1.2(-1.8 to -0.1) -0.9(-1.7 to -0.0) -0.9(-1.7 to -0.0) P-value <0.0001 <0.0001 <0.0001 0.009 Table 4.4: Growth comparison of HAZ at ART initiation and at 12, 24 and 36 months HAZ GROWTH COMPARISON 0 Baseline 12 mo 24 mo 36 mo -0.5 -1 Z-score -1.5 -2 -2.5 -3 Age Figure 4.8 Growth Comparison of HAZ at ART initiation and at 12, 24 and 36 months. H A Z G R O W T H C O M P R I S O N <2 Z-score >2 Z score 0 BASELINE 12MO 24MO 3 6 M O -0.5 -1 Z SCORE -1.5 -2 -2.5 -3 -3.5 AGE Figure 4.9 Growth Comparison of HAZ at ART initiation and at 12,24 and 36 months. Age0-6 Age 6-12 Age 12-24 Age 24-36 4.2.3 Weight-for-height Twenty five percent of children were wasted at the start of ART, which was less common than stunting (62%) and UWA (55%) (Table 4.1). Three years after starting ART most of the children in our study population had reached the median WHZ score for age. There was no significant difference in WHZ between the children initiated on ART in the period 2004 -2007 and those initiated between 2008 and 2010, p=0.23. WHZ increased steadily on ART initiation and also plateaued after one year on ART. There was also no significant difference with increase in WHZ in terms of gender at any time period after ART initiation. Children who were wasted (WHZ< -2) had a faster increase in WHZ in the first 12 months post ART initiation compared to those who were not wasted: They started at -3.1(IQR: - 4.3 to -2.6) and -0.4(IQR: -1.1 to 0.5) and increased to 0.2 (IQR -0.9 to 0.9) and 0.3(IQR- 0.6 to 1.3) respectively. As with WAZ, children less than 12 months of age pre-treatment had a lower WHZ when compared to those older than 12months. This indicates that younger children were sicker than older children when initiating ART. Wasting recovered completely after a year on ART and after three years of follow-up there was no difference in the prevalence of wasting between the different age groups. Table 4.5 Median (IQR) WHZ at Baseline, 12 months, 24 months and 36 months after ART initiation: N= 292 Baseline (0) WHZ at 12months WHZ at 24months WHZ at 36months All Patients N(292) -0.9(-2.0 to 0.2) 0.3(-0.7 to 1.14) 0.2(-0.7 to 0.9) 0.0(-0.7 to 0.7) Gender: Males -0.9(-2.1 to 0.3) 04(-0.6 to 1.3) 0.2(-0.6 to 1.0) -0.0(-0.8 to 0.6) Females -0.9(-2.0 to 0.0) 0.1(-0.8 to 0.9) 0.1(-0.7 to 0.9) 0.1(-0.8 to 0.5) P value 0.89 0.13 0.51 0.19 Initiation of ART in 2004- 2007 -0.8(-1.7 to 0.1) 0.4(-0.7 to 1.2) 0.2(-0.6 to 0.9) -0.1(0.8 to 0.5) Initiation of ART in 2008- 2010 -1.1(-2.5 to 0.3) 0.3(-0.6 to 1.1) 0.2(-0.6 to 0.9) 0.2(-0.6 to 0.8) P value 0.23 0.74 0.77 0.23 Age category at initiation 0-6 months -1.3(-2.5 to -2.1) 0.1(-0.9 to 0.860 0.1(-0.7

to 0.6) 0.0(-0.8 to 0.6) 6-12months -1.5(-3.0 to -0.3) 0.2(-0.9 to 1.1) 0.2(-0.8 to 1.0) 0.1(0.8 to 0.7) 12-24months -0.9(-1.8 to -0.1) 0.2(-0.6 to 1.2) 0.2(-0.7 to 1.0) 0.0(-0.6 to 0.9) 24-36months -0.1(-1.1 to 0.7) 0.8(-0.2 to 1.4) 0.2(-0.4 to 0.9) * P- value <0.0001 0.084 0.93 0.81 <-2 Z score -3.1(-4.3 to -2.6) 0.2(-0.9 to 0.9) 0.1(-1.2 to 1.0) 0.0(-0.8 to 0.5) >-2 Z score -0.4(-1.1 to 0.5) 0.3(-0.6 to 1.3) 0.2(-0.5 to 0.9) 0.1(-0.7 to 0.7) P value <0.0001 0.0003 <0.0001 0.0006 Table 4.5: Comparison of Growth: WHZ scores compare growth with regards to WHZ scores at ART initiation and at 12, 24 and 36months. * No WHZ were available for the children starting ART at 24-36 months of age as they were >5 years old 36 months later and therefore no values were generated 1 0.5 0 Z scores -0.5 -1 -1.5 WHZ Growth Comparison Baseline 12mo 24mo 36mo Age0-6 Age6-12 Age12-24 Age24-36 -2 Age Figure 5.0 Growth Comparison of WHZ at ART initiation and at 12, 24 and 36 months. H A Z G R O W T H C O M PA R I S O N <-2 >-2 Z-SCORE 0.5 0 -0.5 -1 BASELINE 12MO 24MO 3 6 M O -1.5 -2 -2.5 -3 -3.5 AGE IN MONTHS Figure 5.1 Growth Comparison of WHZ at ART initiation and at 12,24 and 36 months. Chapter 5: Discussion This study evaluated 292 HIV-infected children who were initiated on ART at Empilweni HIV Clinic at RMMCH between January 2004 and 31 August 2010. The main findings of this study show that the was a noticeable significant difference in WAZ, HAZ and WHZ at initiation of ART (p<0.0001) with increase in Z scores by 36 months. Even after 3 years of follow up of HIV-infected children on ART, normal values of WAZ and HAZ were not reached, except for WHZ. While younger children (0-12 months at initiation) had lower WAZ scores at initiation, older children (12-36 months at initiation) had lower HAZ scores at initiation. An important factor determining lower 3 years WAZ and HAZ scores was the starting Z-score of <-2. Our findings showed that HAZ and WAZ showed a rapid increase in the first 12 months followed by a more stable growth thereafter for those initiated on ART: WAZ increased from -2.2 (IQR: -3.1 to -1.2) at initiation to just below -0.7 (IQR: -1.4 to -0.1) and HAZ increased from -2.4(IQR -3.6 to -1.4) to -1.7 (IQR-2.7 to -0.7). WAZ scores at initiation of ART were lowest in younger children: -2.6(IQR-3.8 to -1.4) at 0-6months and -2.7(-4.3 to -1.9) at 6-12months. These results we found are in keeping with similar findings of a study done in another cohort in Johannesburg, where it was shown that in the first 12 months of ART treatment, children who were less than 6 months of age at ART initiation had experienced more rapid improvement in WAZ.10 Similar results were also observed in a cohort study in Lilongwe, Malawi in which growth response in HIV- infected children starting ART was studied: the results of this study demonstrated an improvement in growth that occurred after starting ART: median (IQR) WAZ and HAZ increased from -2.1(IQR-2.7 to -1.3) and -2.6(IQR: -3.6 to -1.8) to -1.4(IQR: -2.1 to 0.8) and -1.8 (IQR: -2.4 to -1.1) at 24 months respectively (p<0.001). 8 A different study showed contrary results to the above of a reversed trend of WAZ and WHZ from 2 years onwards, were as the initial analysis of 18000 HIV children in 12 ART programs had revealed an initial improvement in the first year of ART.4 We also found that Z scores at initiation were crucial in predicting growth response, the more severely underweight children showed a more rapid catch-up growth on ART, but did not necessarily reach the same weight as children who had started out with higher values. It is important to asses if height increases beyond 36 months in our population will eventually reach the population norm. Another main finding of our study at RMMCH was that more children were stunted

(62%) than underweight (55%) or wasted (25%). Similar results were also observed in a cohort study in Lilongwe, Malawi in which growth response in HIV-infected children starting ART was studied: the results of this study showed that more than half the children were UWA and that two-thirds were stunted when starting therapy, fulfilling WHO clinical stage 3 or 4.8 Similar findings were also documented in a cohort of 124 HIV-infected Ugandan children who were enrolled and initiated on HAART, their results showed that stunting (HAZ -2.0 (IQR -2.9-1.2)) was more prominent than wasting (WHZ -1.2 (IQR -2.1, -0.5)) at baseline.11 It is of significance that the majority of HIV-infected children were stunted in our study at initiation of ART, as stunting is an indicator of chronicity. 11, 4 Of note, stunting was more prominent in older than in younger children. This finding may be explained by the fact that stunting as a measure of chronicity would be more common in HIV infected children who only access treatment after infancy. In Sub-Saharan Africa, 32 HIV-infected children have been noted not only to be stunted, but to have overall growth retardation early in life: effects on length for age and weight for age by age 3 months compared with values for seroverters were reported in a South African urban cohort. 18 Being underweight for age, a more acute measure of illness was more common in younger children and may be a reflection of their vulnerability to the severe course HIV has been noted to take in early life.11 Another study in South Africa that studied post neonatal deaths under one year of age found peak mortality to be at two to three months.19 This peak was also found to be an indicator of paeditric AIDS in a population with high HIV prevalence. 19 Another study showed 75% survival at 5 months after HIV infection in those infected perinatally and 1.1 years in those children infected postnatally.20 Another main finding of our study was that, age at initiation of ART significantly influenced the amount of growth recovery: lower WAZ were noted at initiation (ranging from -2.7 to -1.4 ($p<0.0001$) from youngest to oldest children) and HAZ starting values (ranging from -3.0 to -1.6 ($p=0.0006$)), but much improvement was noted after initiation of ART with median ranges from WAZ: -0.8 to -0.6 ($p=0.3720$) and HAZ: -1.3 to -1.0 after 3 years follow up. We also found that with regards to WAZ, age at initiation makes a significant difference in the amount of increase in z scores, $p=<0.0001$. However, having a low WAZ is more common at a younger age median -2.6(-3.8 to -1.4) than at the end of 3 years, median -0.9(IQR -1.5 to -0.1). Thus, the final Z-scores was affected more by the baseline Z-scores and not as much by the age. Some studies in African children have also described growth benefits of early age at ART initiation.21,22 One of these, is a study in Kenya amongst HIV-infected children initiated on HAART showed that 12 months post-HAART, children below 3 years had higher increases in WAZ and WHZ following HAART when compared to those 6-10years.21 It was also noted that these younger children also had more rapid catch-up to the population average weight of their peers than older children.21 Although, the specific reasons for more rapid catch up growth where not examined, the findings of our study indicate that children who were UWA or stunted did not manage to reach normal growth after three years of follow-up. The question of whether HIV- infected children initiated on ART with severe growth restrictions ever reach catch-up growth entirely still remains unanswered by our findings. African studies previously done already mentioned above also show an increase in WAZ and HAZ, but without ever reaching normal values.10,6 In contrast to this, a study involving American children who were

not yet on ART, showed that a normal WAZ was reached after one year and normal HAZ was reached after two years of ART initiation.23 Our findings were of the contrary in that even after 3 years of follow up, normal WAZ and HAZ were not attained. This study also included much older children, with ages ranging from 0.4 -16,3 years as compared to our study were the ages ranged from 7- 23 months and had better baseline characteristics as evidenced by median WAZ of -0.74, HAZ -1.22 when compared to ours of WAZ of -2.1 and HAZ of -2.3.23 This has been found to be a normal reaction to the correction of growth retarding disorders; catch-up growth has been shown to firstly affect weight and then height.23 A study in Johannesburg showed that catch-up growth with regards to weight was faster initially, but catch up growth in height was more constant and continued over the two year time period.10 Our findings were also similar when we compared growth in weight and height continuing over a three year period to this study in Johannesburg. In our study, although an increase in height occurred, it however occurred at a more gradual rate when compared with weight as shown by the steady but sure improvement in the medians done pre-treatment at 12, 24 and 36 months. We also noted in our study that WAZ<-2 was more common in young children whereas stunting was more common in older children. Both baseline WAZ<-2 and HAZ<-2 have a lasting effect and both suggest that ART before the advent of UWA or stunting is critical. Three years after starting ART, most of our study population's WHZ had reached the mean Z-score for age where as WAZ and HAZ did not reach the population norm. Children, who started off with WAZ and HAZ less than 2, had catch-up growth ending closer to the population mean than children with less depressed growth pre-treatment. We also looked at the differences in the WAZ, HAZ and WHZ with regards to gender as it has been reported to affect growth in the context of HIV treatment.13A study in a South African cohort showed that pre-randomization to receiving ART, WAZ for boys and girls increased rapidly and WAZ for boys was greater than that for girls, however no statistically significant sex differences where noted post randomization to receiving different ART regimens.13 A different study of older children, reported higher rates of stunting in boys when compared to girls.23 Our study found that there were no significant sex differences noted when comparing WAZ, HAZ and WHZ at baseline and over the first three years of treatment. Less is known about these gender differences when it comes to 35 disease progression and response to ART among children.6 Further investigations regarding gender and the effect on growth in HIV-infected children on ART are warranted. A limitation to the study is that growth failure has many causes, as mentioned previously, it can be caused by: environmental, endocrine factors and genetic factors.3, 4 These factors were not accounted for in our study and could have been confounding factors in our results. Children with pathology in addition to HIV have not been excluded, but it is anticipated that the incidence of primary growth disorders would be low. We also did not investigate known potential pathways for growth differences, such as immune activation, gastrointestinal or neuroendocrine abnormalities or dietary practices. 10 Similar to studies done prior to this, we also think it is unlikely that diet or nutritional factors would vary between children initiating therapy at different ages and would not significantly impact the results.10 Another confounding factor to consider in this research is that children younger than six months of age were some of the sickest children as shown by their being the largest number of children who were UWA and stunted

and thus presenting earlier with poor growth and severely affected growth parameters when compared to older children. ART treatment guidelines changed over time, resulting in the likelihood that children initiated in the earlier years of the roll-out were more likely to have worse baseline characteristics than those in later years. If sicker patients are more likely to get lost, our study had an exclusion criterion for those children who were lost to follow-up. It has been previously revealed that mortality is high among patients who get lost to follow-up. 4 Abacavir use was initiated in 2010 in place of d4T and this could potentially have resulted in different growth changes.16 We did not look for differences between patients on different ART 36 regimens. There also could have been differences between patients on efavirenz compared to those on lopinavir/ritonavir. We also did not compare the growth of our HIV- infected children to HIV-negative children and did not adjust our growth parameters to normal growth patterns for baseline characteristics. Enrollments weights were comparable with age and sex adjusted norms in a study looking at growth in HIV-infected children receiving ritonavir-containing ART, but subjects receiving ritonavir-containing ART were found to be significantly shorter (mean Z-scores, -0.57[29th percentile); 95% CI, -0.73 to -0.40].24 It would have been beneficial to look at head circumference in these children but we were unable to do this due to inadequate data capturing of head circumference. Our study demonstrates that early initiation of ART in HIV-infected children results in an improvement in their overall growth and plays a crucial role in their growth recovery. Despite the challenges of initiating ART in HIV-infected infants in a developing and low- resourced country, the importance of initiating ART as soon as possible after birth cannot be overemphasized. The above results are further confirmed by results from the CHER study in which early initiation of ART led to 76% reduction in mortality and 75% reduction in HIV disease progression.12 A study in a similar cohort in Johannesburg also supports the above evidence, this study showed that the initiation of ART before 6 months of age was associated with faster growth recovery in South African children who were perinatally infected with HIV. 10Another study in Kenya showed that among 43 infants, 47% and 67% were reported to have achieved viral suppression after 6 months of HAART.25 Conclusion In this study, it was shown that initiation of ART has a positive effect in the over-all growth of HIV-infected children. The recovery of WAZ and WHZ is much faster than the recovery of HAZ, but a plateau in growth occurred for all these growth parameters. Similar to other studies, the improvement in height lagged behind to weight and weight for height. Despite sustained growth response and catch up growth in children with advanced HIV disease treated with ART, normal weights and heights are not achieved in 3 years. Age at initiation affected growth recovery in that younger children (0 to 12months) were more severely affected at initiation had an increase in Z-scores and recovered to equal levels whilst children of any age with severe growth indicators at initiation did not catch up to their counterparts. Our study reinforces the need to diagnose HIV and start ART as early as possible to avoid permanent adverse effects on growth. Recommendations ? Recommending earlier and earlier initiation of ART with regards to age, as early initiation of ART has been shown to have a positive over-all effect on growth and can prevent stunting. ? Further studies looking at the growth of infants initiated on ART soon after birth. References 1. UNAIDS. HIV Program in South Africa Factsheets. Available at: http://www.unaids.org/en/regionscountries/countries/southafrica.

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