Comparison of weight gain to age- and sex-specific norms in children 2 to 10 years old on highly active anti-retroviral treatment

J Scholtz

orcid.org/ 0000-0001-7943-567X

Dissertation submitted in partial fulfilment of the requirements for the degree *Master of Science* in Nutrition at the North-West University

Supervisor: Prof HS Kruger

November 2017

Student number: 13027794

ACKNOWLEDGEMENTS

My heart breaks for the children who are born into this world in pain. God gave us free will, but He is not blind to your suffering. Life on earth is temporary, but in Him you will have everlasting life, you will be cherished. You are free because you belong to HIM.

Firstly, I would like to thank Prof Salome Kruger, my supervisor, for your humble heart and for treating me like a gem. Thank you for setting the perfect standard of guidance – I can only hope to follow in your footsteps with my students. I have the deepest respect for you and for the work that you have done in the field of Nutrition.

Thank you Prof Suria Ellis for your expertise and assistance, especially with the statistics of this project.

Thank you Mary Hoffman for helping me to express myself in proper English in my manuscript.

Dearest Sister Katy Mafotsa, managing nurse of the anti-retroviral clinic where I collected data, you have a heart of gold! You are a warrior woman of God and I am sure that you change the lives of people daily because of who you are. Thank you for all your time and help.

Thank you to my employer, Sefako Makgatho Health Sciences University for supporting my research.

Thank you to my parents, *ma* Des and *pa* Otto, for the opportunities that you have given me in life. Thank you for pushing me when I needed pushing, and I did. Thank you for all your hard work and never-ending love. To the coolest brother, Rouan, you are my best friend and you mean the world to me. Nicole, little Lily and *nuwe sussietjie*, that includes you too. I love you all so much!

And Foremost to my husband and little girl, thank you Corné, *my liefste*, for having the kindest, most beautiful heart, for all your support. Thank you for loving me unconditionally. Milandi, *my engeltjie,* God brought you into our lives while I worked on this project. We have the deepest love for you! May you discover yourself in Him and may you know Him in all that you attempt. Let your little light shine my angel. I love you both so, so much!

One thing I have asked of the Lord, and that I will seek:
That I may dwell in the house of the Lord [in His presence] all the days of my life,
To gaze upon the beauty [the delightful loveliness and majestic grandeur] of the Lord
And to meditate in His temple. Psalm 27:4 [AMP]

ABSTRACT

Background: Growth charts are essential tools used for the evaluation of children's health and nutritional status. Growth monitoring has been used to identify children who may require highly active anti-retroviral therapy (HAART), especially in resource-limited settings where treatment decisions are often made on growth data alone. Growth reference data that is used to establish growth charts are most often obtained from populations where growth was optimal, however, growth failure is a hallmark of human immunodeficiency virus (HIV) infection in the peadiatric patient. Inadequate weight gain might warn of clinical deterioration in children infected by HIV, but existing references for optimal weight gain and determining of response to treatment in children initiated on HAART at different ages are not being widely implemented. Interpretations from growth chart evaluations will ultimately have important implications for the treatment of individual children and for child health programmes.

Objectives: The objectives of the study were to assess and analyse the weight gain and weight gain patterns of children younger than ten years old, from initiation of HAART to 6, 12, 18 and 24 months' follow-up after HAART initiation. This study also compares the interpretations of weight gain patterns of the same group of children according to two different weight monitoring reference charts: age- and sex-specific charts developed to assess the growth and response to treatment of children on HAART and weight pattern interpretations according to current World Health Organization (WHO) weight-for-age z-scores (WAZ).

Methods: This project was approached in a quantitative, descriptive-comparative manner with a retrospective design. Weight and other data relating to HIV were captured from patient records kept from the time that an infant/child was initiated on HAART. The weight gain recorded of boys and girls younger than ten years old, during the 24 months following HAART initiation, was assessed and analysed. Descriptive statistics were used to describe the baseline and follow-up characteristics of the boys and girls. Mixed model analysis was also used to test for significance of increases in weight, WAZ, serum-haemoglobin (Hb) and percentage T-lymphocyte-bearing CD4 receptor (CD4%). Mixed methods analysis of longitudinal data was performed, using the restricted maximum likelihood (REML) function with an unstructured covariance type. The quality of fit was estimated by Akaike's information criterion (AIC). Repeated comparisons were made to test for changes between six-monthly follow-up visits, with Sidak adjustment for multiple comparisons. A Kappa test for agreement between the four identified growth pattern categories according to the two growth norms was performed. The Kappa test was also repeated in a subgroup analysis, where only children with a low weight at HAART initiation were included, as defined by WAZ-score < -1. The range of deviations from the norms is presented and the effect sizes of the differences were calculated as mean

difference divided by standard deviation of the mean weight gain at 24-month follow-up for each age group of boys and girls.

Results: The total number of baseline and follow-up data points that formed part of the statistical analyses was *N* = 363, which was derived from 98 infants/children. More than half of the children in this study were underweight and stunted for their age by the time that HAART was initiated. There were statistically significant improvements in weight gain over the 24-month research period and at each six-month follow-up visit since HAART was initiated. Weight gain improved significantly from as early as six months and linear growth started improving significantly after six months. The children in our study did not reach complete catch-up growth after 24 months.

The interpretations of weight gain patterns between the two reference charts that were used: according to the WHO charts, 69% of the children had an increase in rate of weight gain versus only 16% according to the age- and sex-specific weight gain charts. These interpretations were comparatively statistically different, as proven by the poor agreement between the two growth patterns. The results of the subgroup analysis also indicated that the two growth charts were very different in terms of agreement between interpretation outputs.

Discussion, conclusion and recommendations: Even though the children in this study were severely immunocompromised when HAART was started, they showed rapid weight and height improvements. The children did not manage to reach complete catch-up growth within the 24-month research period, which indicated that the unique environment and socio-economic setting of the cohort affected the rate of growth of infants and children. Regarding the weight gain interpretations; the poor agreement between the WHO- and the age- and sex-specific weight gain charts established by Yotebieng *et al.,* (2015) prove that children's weight gain, and growth should be interpreted by using appropriate references, especially if they are available, otherwise we risk making invalid interpretations. Timing is important, especially when it comes to the care and monitoring of young infants/children and particularly in settings where blood cannot be drawn or analysed. A simplified version of expected weight gain in infants/children on HAART, as established by Yotebieng *et al*., (2015) should be created and provided to parents/caretakers, together with education, so that they can also monitor their infants/children at home. It might be necessary also to create monthly or three-monthly weight gain references for healthcare professionals, so that weight can be monitored more often and not just six monthly on average. Regular weight monitoring could aid in improving the infant's/child's outcome through timeous intervention decisions, whether these are social interventions, feeding programmes, special counselling or the improvement of interdisciplinary treatment in any setting.

More nutritional research is needed to determine the impact of nutrition interventions, especially during the early stages of improper weight gain, in order to assess the impact on HAART treatment success and immunity. Length/height gain references have not been established and future research should investigate its association with HIV progression.

Key terms: HIV, infants, children, weight, height, HAART, growth charts, WAZ, catch-up growth, WHO stage, Hb, CD4+%

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LIST OF ABBREVIATIONS

%	Percentage
3TC	Lamivudine
ABC	Abacavir
AIC	Akaike's information criterion
AIDS	Acquired immunodeficiency syndrome
ALT	Aminotransferase
ANC	Antenatal care
ART	Anti-retroviral therapy
ARV	Anti-retroviral
AZT	Zidovudine
BMI	Body mass index
CCMT	The Comprehensive HIV and AIDS Care, Management and Treatment Plan
CD4+	T-lymphocyte-bearing CD4 receptor
CD8+	T-lymphocyte-bearing CD8 receptor
CDC	Centers for Disease Control and Prevention
DGMAH	Dr George Mukhari Academic Hospital
DNA PCR	Deoxyribonucleic acid polymerase chain reaction
EFV	Efavirenz
EPI	Expanded program on immunization
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
FBC	Full blood count
GI	Gastrointestinal
HAART	Highly active anti-retroviral therapy
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HREC	Health Research Ethics Committee (of NWU)
IeDEA	The International Epidemiological Database to Evaluate AIDS
IGF-1	Insulin-like growth factor-1
IgG	Immunoglobulin G
IL-1	Interleuken-1
IL-6	Interleuken-6
IRIS	Immune reconstitution inflammatory syndrome
Kg	Kilograms
LBM	Lean body mass
L/HAZ	Length/height-for-age z-score
LPV/r	Lopinavir/ritonavir

MTCT	Mother-to-child transmission (of HIV)
MTSF	Medium Term Strategic Framework
MUAC	Mid-upper arm circumference
MGRS	Multicenter Growth Reference Study
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCHS	National Centre for Health Statistics
NDOH	National Department of Health (South Africa)
NHANES	National Health and Nutrition Examination Survey
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
NWU	North-West University
PEM	Protein-energy malnutrition
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission (of HIV)
POPD	Paediatric out-patient department
REE	Resting energy expenditure
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
RtHB	Road-to-Health booklet
SMU	Sefako Makgatho Health Sciences University
SMUREC	Sefako Makgatho Health Sciences University Research Ethics Committee
SPSS	Statistical Package for the Social Sciences
TAC	Treatment action campaign
TDF	Tenofovir
TNF-α	Tumour necrosis factor-α
TB	Tuberculosis
US	United States
VL	Viral load
VF	Virological failure
VS	Viral suppression
WAZ	Weight-for-age z-score
WHZ	Weight-for-height z-score
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND AND PROBLEM STATEMENT

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is a global epidemic, with children being heavily affected. UNIAIDS data from 2016 indicate that 36.7 million people were living with HIV globally, of which 2.1 million is children younger than 15 years old. Statistics indicate that 17 million people (46.3% of the known infected population) are receiving anti-retroviral (ARV) therapy. Eastern and southern Africa remains the world's most burdened region (UNIADS, 2017). South Africa, part of sub-Saharan Africa, has the largest epidemic in the world, with 7.06 million people living with HIV during middle 2017 (UNAIDS, 2017).

It was in 2004 that South Africa's National Highly Active Anti-retroviral Therapy (HAART) Programme was officially rolled out, the largest of its kind globally. Infant and child mortalities were prioritised, along with maternal health and the prevention of mother-to-child transmission (PMTCT) of HIV (Maartens & Goemaere, 2014). Currently, all HIV-exposed infants and children less than five years of age are eligible to receive HAART in South Africa, irrespective of their T-lymphocyte-bearing CD4 receptor (CD4+) count (NDOH, 2015). Since 2004, PMTCT of HIV has made tremendous strides; more than 95% of pregnant and HIV-infected women have access to HAART, which contributed to the 48% reduction of newly infected children from 2010 to 2016 (UNAIDS, 2017). The declines in newly infected infants have been expected as a result of prolonged provision of HAART for infants during breastfeeding, combination HAART for all mothers irrespective of CD4+ counts and the roll-out of a third-line HAART programme (Maartens & Goemaere, 2014). Routine use of HAART during pregnancy has caused a decline in the rates of mother-to-child transmission (MTCT) rates, with national perinatal transmission being below 3% (Adam, 2015). An effectiveness evaluation of the PMTCT programme in South Africa found that the programme was able to reduce early MTCT to 3.5%. These results estimate an 86% reduction in early MTCT annually. However, a survey still found large gaps in current systems that aim to eliminate MCTCT: 61% of HIV-infected infants were born from unplanned pregnancies, 50% of mothers have their first antenatal care (ANC) visits at later than 20 weeks' gestation and there is only 85% ARV coverage of the PMTCT population (Goga *et al*., 2015).

Paediatric HIV infection is associated with growth retardation, both linear and ponderal, as well as delayed sexual maturity. Poor growth may be a major contributor to paediatric malnutrition and morbidity (Venkatesh *et al*., 2010; Merchant & Lala, 2012). The National Consolidated Guidelines for the PMTCT of HIV and Management of HIV in Children, Adolescents and Adults document (NDOH, 2015) state that routine assessment of nutritional status and the monitoring

of a child's growth must be done at follow-up visits. It has also been suggested that growth failure may be an indicator of ARV treatment failure (Mawela, 2007; NDOH, 2015). The World Health Organization (WHO) supports the use of clinical parameters, such as growth monitoring, in environments where viral load (VL) cannot be obtained, especially growth parameters to monitor HAART response (WHO, 2013). Growth monitoring has been used to identify children who may require HAART, especially in resource-limited settings (Weigel *et al.,* 2010; Yotebieng *et al.,* 2010; Benjamin *et al.,* 2004). The proposal that growth monitoring may be a surrogate marker for viral suppression (VS) has been made previously (Benjamin *et al.,* 2003). Weight and height trajectories may even be the only data that can be used to predict HAART response in resource-limited settings (Weigel *et al.,* 2010; Yotebieng *et al.,* 2010; Benjamin *et al.,* 2004).

Growth charts are essential tools used for the evaluation of children's health status, including their nutritional status, but the consequent decision to intervene (or not) is highly dependent on the "type" of growth chart that was used for the evaluation. This means that interpretations from growth chart evaluations will ultimately have important implications for child health programmes (Turck *et al*., 2013). The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) stated that the 2006 WHO growth *standards* can be used as a universal tool in the assessment of growth of children, because it provides a picture of how a child will grow in an optimal environment. Growth *standards* provide the opportunity to assess the growth of children in relation to healthy breastfed infants worldwide and it provides a baseline for research in child growth comparison (Turck *et al*., 2013). Regarding the WHO 2007 growth *references* (5-19 years), ESPGHAN emphasised that national bodies must finally decide whether or not to implement these growth references, because growth patterns during the 5- to 19-year period differ between populations. The growth of children in this age group is influenced by ethnicity, culture, environment, socio-economic status and availability of healthy nutrients (Turck *et al.,* 2013).

The growth of HIV-infected children who have been identified and initiated on HAART in South African provincial hospitals and clinics is currently being assessed and monitored by healthcare professionals, using any available resources. The road-to-health booklet (RtHB) is provided to community clinics and is used for the recording of various health factors, and include two WHO growth charts for infants and children from birth to five years old (NDOH, 2016), but research indicates that the WHO growth charts (in the RtHB) that are used in the provincial hospitals and clinics are invalid for monitoring changes in weight in children on HAART (Yotebieng *et al*., 2010; Yotebieng *et al*., 2015), because the healthcare professional will not be able to meaningfully interpret the response to treatment on a growth chart that has been constructed for a different (healthy) population (Turck *et al.,* 2013). Owing to time constraints, raw values are also sometimes recorded instead of derived indicators, to little effect (Duggan, 2010). The need for special growth norms that can be used for the HIV-infected child on HAART is being

acknowledged. Even though the WHO growth charts are stratified according to age and sex, these growth standards and references were established using values of growing HIV-uninfected children. Furthermore, the growth curves on the WHO growth charts start at birth, whereas HAART can be initiated at any age. It is the growth from initiation of HAART that we are interested in, not the growth from birth (Yotebieng *et al*., 2015).

A change in nutritional status might warn of clinical deterioration in HIV infection (Duggan, 2010). Weight change is strongly associated with HAART treatment outcomes (Yotebieng *et al*., 2010; Yotebieng *et al*., 2015). In 2015, Yotebieng *et al*. constructed specialised weight gain norms for children on HAART. In addition, these norms are also age- and sex-specific and may serve as a useful clinical tool to monitor treatment, especially because weight gain is a sensitive indicator of treatment failure in African children on HAART (Kekitiinwa *et al.,* 2013).

If the holistic management of the HIV-infected child were to be based on an *objective* anthropometrical assessment component of nutritional status, then the quality of life of that child could be improved (Duggan, 2010). The objective anthropometrical assessment of HIV-infected children on HAART can influence decisions and advocacy regarding nutritional supplementation for HIV-infected children (Duggan, 2010). Age- and sex-specific normative curves may aid in the identification of poor response to HAART in children, especially in the first year following initiation (Yotebieng *et al*., 2015). This means that monitoring weight gain on specialised growth charts could be related to better outcomes of children on HAART, above and beyond describing average growth.

This study serves as a logical extension of the work that was done by Yotebieng and co-workers (2010, 2015) who constructed weight gain norms for HIV-infected children on HAART. This study will also provide valuable information on the weight gain patterns of children below the age of 10 years who have been initiated on HAART.

1.2 AIMS AND OBJECTIVES

This study aimed to assess the weight gain and weight change patterns of children younger than ten years of age, initiated on HAART and monitored primarily in terms of weight changes over a period of at least 18 months, aiming for 24 months. The researchers also applied newly proposed weight-gain norms for HIV-infected children on HAART in order to gain age- and sex-specific interpretations of these children's growth patterns. The children's weight data and other contributing factors were collected from patient files at the paediatric HIV clinic of Dr George Mukhari Academic Hospital (DGMAH) in Ga-Rankuwa, South Africa. Growth assessment comparisons between current routine growth charts used at this clinic and the newly proposed age- and sex-specific weight-gain norms were also done. The findings could help to determine

whether the interpretation of current weight gain is meaningful in terms of potentially providing nutritional services to impact on weight gain and possibly also on the progression of HIV infection.

The objectives of the study were:

a) To assess and analyse the weight gain and weight gain patterns of children from initiation of HAART and again at 6, 12, 18 and 24 months follow-up visits to the paediatric HIV clinic at DGMAH, by plotting weight changes after HAART initiation on new proposed weight-gain norms (Yotebieng *et al.,* in 2015).

b) This study also compares the interpretations of weight gain patterns after HAART initiation of the same group of children according to two different weight monitoring charts; age- and sex-specific HIV charts, proposed by Yotebieng *et al*., (2015) and weight pattern interpretations according to current WHO weight-for-age z-scores (WAZ).

1.3 STRUCTURE OF DISSERTATION

This mini-dissertation is divided into five chapters, in which the current Chapter 1 as the introduction consists of a background and problem statement as well as the study aims and objectives. Chapter 2 includes a literature review describing the topic in full and referencing relevant literature. Chapter 3 consists of the methodology of the study. In Chapter 4, the study is described in article format as a research paper, containing an abstract, introduction, materials and method, results, and a discussion and conclusion section. In Chapter 5, a summary of the essential findings, a conclusion and recommendations are given. All forms and referral letters that were used and obtained during the course of the study are included in the Addendums, displayed as Addendum A to E. The approval letter from the North-West University (NWU) Health Research Ethics Committee (HREC) can be found in Addendum A. Chapters 1,2,3 and 5 are written according to South African English spelling and the NWU guidelines, with references in text and reference lists according to the reference guidelines of the NWU. Chapter 4 follows United Kingdom English spelling and the style of writing and referencing follows that of the selected journal in which the article is intended to be published. Author guidelines for the South African Journal of HIV Medicine can be found in Addendum E.

1.4 CONTRIBUTION OF AUTHOR

The author was involved in the data collection process of the study, in addition to being responsible for literature searches, statistical analysis of data and the writing of the manuscript.

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CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

The numbers of people who are infected with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in South Africa, has decreased from 500 000 in 2005 to 380 000 in 2010. A further decline to 270 000 people, was reported in 2016 (UNICEF, 2017). The number of children in South Africa who is being treated with highly active anti-retroviral therapy (HAART) has increased from 29% in 2010 to 55% in 2016 (UNICEF, 2017). The amount of people who are living with HIV and AIDS has increased from 5.1 million in 2005 to 7.1 million in 2016, because more people are receiving HAART and living longer (UNICEF, 2017). With South Africa's National highly active anti-retroviral therapy (HAART) Programme implemented in 2004 being the largest of its kind, it was clear that infant and child mortalities were prioritised, along with maternal health in the prevention of mother-to-child transmission (PMTCT). Great success has been achieved and much has been learnt since the implementation and the later upscaling of the HAART programme (Maartens & Goemaere, 2014). Although the number of AIDS related deaths have declined by 40.7% from 2005 to 2016 (UNICEF, 2017), half of all deaths of infants younger than five years in South Africa in 2011, were associated with HIV infection (Barron *et al.,* 2013).

2.2 HUMAN IMMUNODEFICIENCY VIRUS INFECTION DIMINISHES THE IMMUNE SYSTEM

HIV is a retrovirus that destroys the cells of the immune system and AIDS is the complex disease that results from the HIV infection. The HIV induces cell-mediated immune deficiency, which makes a person susceptible to life threatening diseases and opportunistic infections (Shaw, 2015). The hallmark of HIV infection is the direct infection and depletion of the host's T-lymphocyte-bearing CD4 receptor (CD4+) cells. CD4+ cells are lymphocytes and form part of T-helper cells that play a major role in coordinating the host's immune response by stimulating other immune cells, such as macrophages, B-lymphocytes and T-lymphocyte-bearing CD8 receptor (CD8+) cells, to fight infection. CD4+ cells represent the most intensely affected lymphocyte cell type following HIV infection, but other leukocyte subsets are also altered. Alterations include accelerated cell turnover and cell cycle perturbations, apoptosis and immune senescence. Altered functionality in that sense is also observed for CD8+ cells, B cells and innate immune cells (Ribeiro *et al*., 2002; Paiardini *et al*., 2004).

HIV infection is classified according to clinical signs and symptoms and also according to the patient's immunity. HIV-infected individuals may be affected differently and many

demographical, social, nutritional and genetic factors could influence how this complex virus expresses itself in any one person. The progression of the disease is also very individual, but it is very important to put the pieces of the puzzle together as best we can in order to treat and help each person. Some classification systems have been put in place (WHO, 2006; WHO 2007) to assist with that puzzle.

2.2.1 Clinical staging of human immunodeficiency virus infection

The clinical manifestation of HIV/AIDS and its progression is different in children when compared with adults, because of the still immature immune system, which allows for greater dissemination in the various organ systems (Merchant & Lala, 2012). Clinical classification of HIV in children in South Africa is based on the World Health Organization's (WHO) staging system, which was updated in 2006 (WHO, 2006; WHO, 2007). Another staging system that is used is the clinical staging system of the United States (US) Centers for Disease Control and Prevention (CDC) (Caldwell *et al*., 1994). The CDC staging system is less applicable in developing countries because clinical staging categories are based on bacterial cultures, virology and fungal identifications done in laboratory facilities, as well as more invasive investigations such as lung puncture, bronchoscopy and imaging techniques which are not practical in developing and rural settings (Bakaki *et al*., 2001).

Clinical staging is important and forms the basis of treatment options. It also strengthens the clinical diagnosis, especially when laboratory testing is not available, and provides the clinician with a better idea of HIV disease progression (Mawela, 2007). The four-stage WHO system for paediatric HIV infection is provided in Table 2.1, and ranges from asymptomism and persistent generalised lymphadenopathy to severe wasting and stunting, encephalopathy, tuberculosis (TB), nephropathy, cardiomyopathy and other disorders (WHO, 2006; WHO, 2007).

Some of the common early clinical manifestations of HIV infection have been identified as the following: generalised lymphadenopathy, hepatosplenomegaly, recurrent or persistent diarrhoea and protein-energy malnutrition (PEM) (Merchant *et al*., 2001; Merchant & Lala, 2012).

Table 2.1 WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1
Asymptomatic, persistent generalised lymphadenopathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly, popular pruritic eruptions, fungal nail infection, angular cheilitis, lineal gingival erythema, extensive wart virus infection, extensive molluscum contagiosum, recurrent oral ulcerations, unexplained persistent parotid enlargement, herpes zoster, recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)
Clinical stage 3
Unexplained moderate malnutrition or wasting not adequately responding to standard therapy, unexplained persistent diarrhoea (14 days or more), unexplained persistent fever (above 37.5 ºC intermittent or constant, for longer than one month), persistent oral candidiasis (after first 6-8 weeks of life), oral hairy leukoplakia, acute necrotising ulcerative gingivitis or periodontitis, lymph node tuberculosis, pulmonary tuberculosis, severe recurrent bacterial pneumonia, symptomatic lymphoid interstitial pneumonitis, chronic HIV-associated lung disease including bronchiectasis, unexplained anaemia (< 8g/dL), neutropaenia (<0.5 x 10^9/L) and/or chronic thrombocytopaenia (<50 x 10^9/L)
Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy, pneumocystis pneumonia, recurrent severe bacterial infections (such as empyema, pyomyositis bone or joint infection or meningitis but excluding pneumonia), chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site), oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs), extrapulmonary tuberculosis, Kaposi sarcoma, cytomegalovirus infection: retinitis or cytomegalovirus infection: another organ with onset at age older than one month, central nervous system toxoplasmosis (after one month of life), extrapulmonary cryptococcus (including meningitis), HIV encephalopathy, disseminated endemic mycosis (coccidiomycosis or histoplasmosis), disseminated non-tuberculous mycobacterium infection, chronic cryptosporidiosis (with diarrhoea), chronic isosporiasis, cerebral or B-cell non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy, symptomatic HIV-associated nephropathy, HIV-associated cardiomyopathy

From: WHO, 2007:15-16.

2.2.2 Immunological staging of human immunodeficiency virus progression

Immunological staging was developed by the CDC and is based on CD4+ cell count, specifically CD4+ cell percentage in infants and children up to six years of age. CD4+ cell numbers change rapidly during early childhood and approach "adult" numbers only around six years of age (Jaspan *et al*., 2005). The CDC immunological classification system based on age-specific CD4+ T-cell count and percentage is also commonly used to categorise the level of immune suppression, ranging from no suppression (≥ 25% in 2-10 year olds) to severe suppression (< 15% in 2-10 year olds) (Shaw, 2015). Viral suppression (VS) is highly predictive of CD4+ recovery (Zanoni *et al*., 2012; Kovacs *et al*., 2005; Machado *et al*., 2007). Immunological staging is utilised in considering treatment options (Mawela, 2007). Immunological staging of young children is provided in Table 2.2 (WHO, 2007). HIV infection in the paediatric patient differs from that of the HIV-infected adult. Viral loads (VL) are much higher in the first year of life and start declining to values similar to that of adult cohorts only by age two to three years (Jaspan *et al*., 2005). Some previous studies have indicated that advanced immunological disease and increased VL are associated with poor growth in HIV-infected children (Pollack *et al*., 1997; Johann-Liang *et al*., 2000).

Table 2.2 WHO immunological classification for established HIV infection

HIV-associated Immunodeficiency	Age-related CD4+ values			
	<11 months (%CD4+)	**12-35 months (%CD4+)**	**36-59 months (%CD4+)**	**>5 years (absolute number per mm^3 or %CD4+)**
None/not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or 15%

From: WHO, 2007:15.

2.3 EXPOSURE, DIAGNOSIS AND MEDICAL MANAGEMENT OF HUMAN IMMUNODEFICIENCY VIRUS IN INFANTS AND CHILDREN

Infants and children acquire HIV mostly via vertical perinatal transmission during pregnancy, labour, delivery and incorrect breastfeeding practices (Shaw, 2015; Mawela, 2007). Vertical transmission rates remain high, especially in the absence of anti-retroviral treatment (ART), leading to high rates of infant morbidity and mortality (Adam, 2015). Previous research

suggests that if intrauterine infection coincides with the period of rapid proliferation of CD4+ cells, then the HIV could infect the majority of immunocompetent cells within the developing foetus (Abuzaitoun & Hanson, 2000), which is why infants have rapid disease progression in the first months of life (Newell *et al*., 2004), highlighting the importance of early identification, diagnosis and management. The challenge is that passively acquired transplacental immunoglobulin G (IgG) antibodies may persist for up to 18 months, which means that infection can be confirmed only after 18 months of life, using virological assays. The detection of antibodies after the first year of life is said to be highly predictive of HIV infection, but is not conclusive. To detect HIV infection in an HIV-exposed infant before 18 months of age will require specific testing for HIV Deoxyribonucleic acid (DNA) via the qualitative polymerase chain reaction (PCR) test. A quantitative HIV ribonucleic acid (RNA) (viral load assay) must be performed to confirm a positive HIV DNA PCR (NDOH, 2015). An HIV DNA PCR test that is conducted on an HIV-exposed infant at birth may identify 30-50% of HIV infected infants. Evidence of viral infection is seen as early as days to weeks after birth (Mawela, 2007). A rapid HIV antibody test is done after 18 months of age (NDOH, 2015).

Breastfeeding also plays a role in the diagnosis of HIV in an infant or child. A non-breastfeeding HIV-positive mother can have a HIV DNA PCR test done after six weeks of birth of the infant with 100% sensitivity (Nielsen & Bryson, 2000), but the gold standard of diagnosing HIV infection, according to South African guidelines (NDOH, 2005), remains two concordant HIV DNA PCR tests, conducted at six weeks and four months of age. If a child is breastfed, the HIV DNA PCR test must be done again six weeks after cessation of breastfeeding. If a first test is positive (no concordant test done, yet), then the result must be interpreted in the context of the clinical classification seen in that infant (Mawela, 2007).

The WHO Clinical Criteria for presumptive diagnosis of HIV in infants and children less than 18 months of age consists of the presence of the HIV antibody as well as an AIDS-indicator condition. If the infant or child is symptomatic with severe pneumonia, oral thrush or severe sepsis, then this may also serve as a presumptive diagnosis (Merchant & Lala, 2012). Some additional clinical features that may be associated with HIV infection before the age of six months include oropharyngeal candidiasis, dermatological disorders, ear discharge and lobar consolidation, as identified in an African study (Bakaki *et al*., 2001).

In South Africa, the medical management of the HIV-infected (or suspected infected) infant or child should include: ARV care when appropriate, prophylactic treatment of opportunistic infections, treatment of incidental diseases, routine immunisations (EPI) and pneumococcal vaccines, nutritional care and support and monitoring of growth and development (Mawela, 2007).

2.4 HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND GROWTH

The aetiology of growth retardation and failure, which is a hallmark of HIV infection, is complex and multifactorial. Its complexity is not yet fully comprehended and, furthermore, underlying diseases related to compromised immunity will amplify this growth impairment (Mawela, 2007). Growth monitoring is used to identify children who may require HAART in resource-limited settings (Weigel *et al.,* 2010; Yotebieng *et al.,* 2010; Benjamin *et al.,* 2004), indicating the major impact that this virus has on growth and development. The literature has investigated and hypothesised possible mechanisms and studied growth impairment patterns seen in HIV infected children.

2.4.1 The complexity of growth impairment in human immunodeficiency virus-infected children

Children in developing countries suffer larger numbers of paediatric infectious diseases due to poor sanitation, often poor vaccine coverage and insufficient supportive care facilities and personnel (Stephensen, 1999). An increased frequency of common childhood infections, such as gastroenteritis, pneumonia, TB and ear infections (Merchant & Lala, 2012) as well as the additional high prevalence of malnutrition diagnosed in rural communities exacerbate immunodeficiency and accelerate the progression of the disease (Stephensen, 1999; Chantry & Moye, 2005; Mawela, 2007).

HIV-associated opportunistic infections can cause gastrointestinal (GI) disturbances and malabsorption, which may lead to nutrient deficiencies and subsequently affect growth patterns (Stephensen, 1999; Johann-Liang *et al.,* 2000). Although malabsorption could affect growth in this manner, it has been suggested that this is not the complete explanation, because nutritional support alone does not entirely restore growth failure (Stephensen, 1999). Neuroendocrine abnormalities of the growth hormone and adrenal and thyroid axis (Laue *et al.,* 1990; Kaufman *et al*., 1997), altered lipid metabolisms (Hellerstein *et al*., 1993), as well as chronic viral activity resulting in a chronic pro-inflammatory state, are also linked to growth alterations in children (Johann-Liang, 2000; Miller *et al.,* 2001). Previous research also investigated nutritional deficiencies related to iron metabolism (Blumberg *et al.,* 1984) and protein metabolism (Stein *et al*., 1990).

An interesting study conducted by Johann-Liang *et al*. (2000) in New York aimed to determine the relationship between energy metabolism and growth abnormalities in pre-pubertal HIV-infected children and that of HIV-infected children with normal growth (1.3 – 13.2 years old). The study also investigated certain laboratory characteristics that have previously been suggested to contribute to growth impairment, namely iron, protein, CD4+ count, VL, insulin-like growth factor-1 (IGF-1) and serum interleukin-6 (IL-6) levels. The findings indicated that resting

energy expenditure (REE) in HIV-infected children is not increased as it is in the HIV-infected adult population. The authors found this in support of previous findings, which indicate that a hypermetabolic state is not the cause of growth retardation in children with HIV infection. One of the chief determinants of negative energy balance in these children was inadequate nutritional intakes (Johann-Liang, 2000), and this is similar to findings in the adult population (McCallan *et al*., 1995). The same study conducted by Johann-Liang *et al*. (2000) found that serum protein levels were lower in HIV-infected children with inadequate growth, which supports the hypothesis that failure to maintain protein balance and abnormal utilisation of protein is associated with growth impairment. Because this study also investigated the cytokine derangement [IL-6, IL-1 and tumour necrosis factor-α (TNF-α)] that has been postulated to play a role in HIV wasting in adults (Navikas *et al*., 1995), the findings were particularly interesting. There were significant differences in plasma IL-6 levels (increased in HIV-infected children with impaired growth versus those with normal growth) and IGF-1 levels. It has been suggested that IL-6 may decrease IGF-1 responses and play a role in poor growth, as results indicated significantly lower levels IGF-1 in HIV-infected children when compared with demographically matched controls. Moreover, HIV-infected children with poor growth also had lower IGF-1 levels than those with HIV and normal growth (Johann-Liang *et al*., 2000). Not many studies in the developing world have investigated laboratory values, growth and intakes like this one, although some shortcomings were that the group of children was not very large (n = 23) and they were studied only at one point of wellness. Larger cohorts would provide a better picture of the contribution of energy expenditure to growth impairment in HIV-infected children (Johann-Liang *et al*., 2000).

HIV infection is therefore associated with growth retardation in infants and children and this may be a major contributor to paediatric malnutrition and morbidity (Venkatesh *et al*., 2010). Impaired growth is a major manifestation of HIV infection in children, ranging from subnormal weight and height patterns for age, leading to eventual wasting and stunting. Growth is a sensitive indicator of disease progression (Mawela, 2007) and it has been suggested that growth correlates with VL in early infancy (Pollack *et al.,* 1997; Bakaki *et al*., 2001), but more recent studies have shown no correlation between weight gain and VS or virological failure VF) (Yotebieng *et al*., 2015).

2.4.2 Growth impairment patterns in human immunodeficiency virus-infected children

Growth retardation, both linear and ponderal, as well as delayed sexual maturity, is associated with paediatric HIV infection (Merchant & Lala, 2012). Weight and height decreases rapidly within the first months of life in HIV-infected infants when compared with their uninfected counterparts with similar growth measurements at birth (Miller *et al.,* 2001). These growth

differences were also highlighted by Venkatesh *et al*. (2010), who found that HIV-infected infants experienced significantly greater growth retardation within three months after birth when compared with HIV-uninfected infants. Another study, conducted in infants from Durban, South Africa, found that HIV-infected infants had early and sustained low mean z-scores by three months of age (Bobat *et al.,* 2001).

Stunting, defined as a z-score of <-2 length-for-age (L/HAZ) is an independent predictor of HIV progression, immune reconstitution and viral replication (Venkatesh *et al*., 2010). The direct impact that infection may have on linear growth may be linked to the induction of the acute-phase response. Pro-inflammatory cytokines such as IL-6, TNF-α and IL-1 may directly affect bone remodelling processes required for long bone growth. HIV infection of osteoclasts or osteoblasts may also impact on long bone growth, as many strains of macrophages could infect these bone cells and affect linear growth (Stephensen, 1999).

Underweight, defined by weight-for-age z-score (WAZ) of <-2 and stunting, defined by a length/height-for-age z-score (L/HAZ) of <-2 (WHO, 2006), may occur simultaneously in the HIV-infected child (Bobat *et al*., 2001). Wasting, defined by weight-for-height z-score (WHZ) of <-2 is also characteristic of HIV-infected children (Venkatesh *et al*., 2010), but often, due to early rapid proportional declines in weight and height, not all study results define wasting in the HIV-infected child early (Bobat *et al*., 2001). Earlier research also suggests that wasting becomes more apparent during advanced stages of HIV-progression (Bailey *et al.,* 1999). When comparing growth patterns in severely malnourished children (HIV-uninfected) with those in severely malnourished HIV-infected children, it is usually seen that weight decreases take place before height decreases. In the infected child, one tends to see decreases in both weight and height at the same time (Venkatesh *et al*., 2010). Research consistently suggests that a simultaneous decrease in weight and height is apparent in early infancy with a relative loss of weight-for-height in late childhood (Merchant & Lala, 2012).

HIV-infected children show a tendency to grow below the healthy standards set for age and sex (Merchant & Lala, 2012). The HIV-infected child, when compared with the uninfected counterpart, may not reach catch-up growth, be it due to changes in metabolism or due to acute infections. Paediatricians, dietitians, clinicians and all other healthcare personnel involved in managing HIV-infected children should now ponder whether growth assessment and more specific, weight gain monitoring, should perhaps be conducted objectively in HIV-infected infants and children, who will grow differently from their healthy counterparts.

2.5 ADDRESSING HUMAN IMMUNODEFICIENCY VIRUS AND CHILD MORTALITY IN SOUTH AFRICA: LIFELONG HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY

The South African National HAART Programme, the comprehensive HIV and AIDS care, management and treatment plan (CCMT), was rolled out on 1 April 2004 in South Africa according to WHO guidelines and is the largest of its kind globally (Davies *et al*, 2009). The South African NDOH implemented the CCMT by providing HAART to eligible adults, pregnant women and children in the public sector as per National Guidelines (NDOH, 2004). At that stage in 2004, 29.5% of women attending public antenatal facilities were HIV infected (Meyers *et al.,* 2006). The life expectancy of adults in rural Kwazulu-Natal, South Africa, increased from 49.2 years in 2003 to 60.5 years in 2011 (Bor *et al.,* 2013). All infants and children with HIV should have access to appropriate HAART as part of the medical management of the disease, according to National Guidelines (Mawela, 2007; NDOH, 2004).

The birth of the CCMT was difficult and delayed and unfortunately, thousands of lives were lost as a result of this delay. Civil society, notably the Treatment Action Campaign (TAC) and the AIDS Law Project helped to force the government at that time to implement ARVs for PMTCT and later, the CCMT – the HAART programme for South Africa (Maartens & Goemaere, 2014). The International epidemiological Database to Evaluate AIDS (IeDEA) reported in 2009 that the CCMT programme demonstrates a significant clinical benefit for those with access (Davies *et al*., 2009). The programme is the largest of its kind in the world, with 3 900 000 people who were on treatment in 2016. The number of children on treatment has increased from 29% in 2010 to 55% in 2016. This is just over half of the number of children who require HAART in South Africa. Poor integration of services, drug procurement and distribution issues, laboratory capacity and a lack of sufficiently trained staff were some of the challenges that South Africa faced after the CCMT programme roll-out (Meyers *et al.,* 2006). These factors may still affect access to treatment as we speak.

Significant contributions have been donated towards the setting up of the CCMT. Donor-funded pilot HAART projects, such as the Khayelitsha project (with funds from the Western Cape government), have helped to improve the feasibility (scaling up) of the CCMT, but the programme is largely funded from the national budget (Maartens & Goemaere, 2014). Before commencement of the CCMT, a substantial number of children could access HAART only through donor-funded programmes (Davies *et al*., 2009).

The reduction of ARV costs negotiated by the NDOH has been one of the biggest achievements as South Africa is a major global market participant because of the size of the CCMT. The CCMT is still expanding, with retention in care and associated proper accountable management of the programme and all its facets being the focus of the next decade (Maartens & Goemaere, 2014).

2.5.1 Prevention of mother-to-child transmission

The timeline or evolution of the PMTCT programme in South Africa started between 1998 and 1999 in two midwife obstetrics clinics in Khayelitsha, Cape Town, despite the lack of national policy. It was in 2002 that the South African government was unsuccessful in challenging the implementation of a national PMTCT programme and the PMTCT programme commenced. In 2003, the government published an operational plan addressing the treatment of those infected with HIV. This plan included the provision of nevirapine (NVP), as well as the up-scaling of care facilities. In 2004, the CCMT was introduced and pregnant women with a CD4+ count of <200 cells/mm^3 were eligible to receive HAART. In 2008, the South African DOH updated the PMTCT policy by including dual prophylaxis NVP and zidovudine (AZT) from 28 weeks' gestation, as well as NVP for the pregnant mother and the infant within 72 hours of delivery. In 2010 the DOH revised the PMTCT policy and included the provision of lifelong HAART for HIV-positive women with a CD4+ cell count <350 cells/mm^3, along with option A of the WHO guidelines (WHO, 2010). Prophylaxis for exposed infants included daily NVP for 6 weeks, also continued in exposed breastfed infants whose mothers were not on HAART, in order to reduce mother-to-child transmission (MTCT) (NDOH, 2010). In 2011 the Minister of Health endorsed a policy that stated that breastfeeding should be prioritised and exclusive in public health facilities (the provision of formula milk was phased out), which commenced in line with a call from global agencies to develop a national action framework to eradicate MTCT (Barron *et al*., 2013).

PMTCT forms part of the CCMT and involves informing, educating and counselling on primary prevention of infection and unintended pregnancy in women and identification of HIV infection in pregnant women. If a pregnant woman is identified as HIV positive, HAART will be provided immediately as prophylaxis for perinatal transmission (Meyers *et al*., 2006). Approximately 29% of women attending antenatal care (ANC) are HIV positive (Adam, 2015).

Impairing viral replication at maternal age is critically important to the foetus in order to prevent vertical transmission of HIV to the unborn baby. This statement was highlighted by a large (3 468 infants/children) African pooled analysis that found that early infant mortality is significantly associated with early HIV infection ("early" being defined as a positive PCR DNA before day three of life followed by another positive result before four weeks of age or only one positive PCR DNA result before four weeks of age). The mortality rates of children who have been infected early are 48% versus 26% in late infection ("late" defined as a positive PCR DNA result on or after four weeks of age) (Newell *et al.,* 2004). Prophylactic care and monitoring to decrease VL in HIV-infected pregnant women are extremely important because high maternal VL's or low CD4+ cell counts (<200 per µl) have been associated with maternal death, which in turn is strongly associated with infant death (Newell *et al.,* 2004). HIV-positive pregnant women

should therefore have a CD4+ cell count done immediately in order to assess whether triple HAART is needed to improve her own outcome as well to prevent perinatal HIV transmission to her unborn baby (Meyers *et al*., 2006).

Single-dose NVP was provided to mothers and newborn infants as part of PMTCT and this was the standard in South Africa from 2003, before HAART was provided to children in 2004 (NDOH, 2015). The current recommended first-line ARV regimen for pregnancy includes lamivudine (3TC), efavirenz (EFV) and tenofovir (TDF). Although this regimen has been used less extensively in pregnancy than NVP and AZT, monitoring remains essential and HAART use during pregnancy is generally safe. Adherence to monitoring and continued counselling remains crucial in preventing the possibility of multi-class resistance in both mother and infant (Adam, 2015).

The successful and routine use of HAART as per the PMTCT programme has to date provided the opportunity for the fertile, HIV-positive woman to become pregnant, expecting a child that could be HIV free and with no more complications during pregnancy than her uninfected pregnant counterpart. The use of HAART during pregnancy has been well researched and robust evidence demonstrating the benefit of HAART for the prevention of MTCT outweighs any potential risks (Adam, 2015).

PMTCT of HIV has made tremendous strides since 2004 because more than 95% of pregnant, HIV-infected women now have access to HAART, which resulted in a 48% decline in newly infected children from 2010 to 2016 (UNAIDS, 2017). Declines in newly infected infants were expected due to prolonged provision of HAART for infants during breastfeeding, combination HAART for all mothers irrespective of CD4+ counts and the roll-out of a third-line HAART programme (Maartens & Goemaere, 2014). Routine use of HAART during pregnancy has caused a decline in the rates of MTCT, with national perinatal transmission being below 3% (Adam, 2015). An effectiveness evaluation of the PMTCT programme in South Africa found that the programme was able to reduce early MTCT to 3.5%. These results estimate an 86% reduction in early MTCT annually. However, a survey still found large gaps in current systems that aim to eliminate MCTCT: 61% of pregnancies that resulted in HIV-infected infants were unplanned, 50% of first ANC visits were made at 20 weeks' gestation and there is only 85% ARV coverage of the PMTCT population (Goga *et al*., 2015).

The routine use of HAART during pregnancy has led to a substantial decrease in maternal morbidity and mortality, which is crucial, since the focus of PMTCT has shifted from preventing perinatal HIV transmission to the well-being of the HIV-positive mother, who is essential in caring for her child (Adam, 2015). Despite the tremendous success in the implementation of the PMTCT programme in South Africa, some challenges remain. These include the routine collection of quality data, as well as the need for mentoring and supervisory systems that can

help facilitate the use of the data effectively. Also, most pregnant women (40%) attend ANC for the first time only before 20 weeks' gestation and some go into labour without ANC exposure. PMTCT policy requires pregnant women to be exposed to ANC early (at 14 weeks' gestation) to start intervention early. Another challenge remains the early testing of infants to ensure fast referral for treatment. It is known that 15% of public health care facilities within South Africa are still not able to facilitate treatment and therefore, the referral of women away from such under-resourced facilities may lead to us losing them altogether (Barron *et al*., 2013).

2.5.2 The effectiveness of highly active anti-retroviral therapy programmes in developing countries

Globally, the success of various HAART programmes has been bitter-sweet. The number of patients receiving treatment has increased 16-fold from 2003 to end 2010, reaching 6.6 million (WHO, 2011), but in 2016, statistics indicated that 44% of people who live with HIV are not on treatment (UNAIDS, 2017). More patients are experiencing treatment failure and viral resistance and the need for more expensive second-line regimens has soared (WHO, 2012). According to UNAIDS, (2017), 45% of people, who are living with HIV, are experiencing VS.

2.6 HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY FOR THE HUMAN IMMUNODEFICIENCY VIRUS-EXPOSED AND -INFECTED INFANT AND CHILD

According to the National Document (NDOH, 2015), all HIV-exposed infants and children younger than five years of age are eligible to receive HAART, irrespective of their CD4+ count. Children between five and ten years are eligible for HAART if they are symptomatic (stage III or IV WHO clinical staging) or if their CD4+ count is< 500 cells/mm^3, irrespective of WHO clinical stage.

HAART slows disease progression by preventing viral replication and thereby decreasing VL in different ways, depending on the class of HAART medication. By providing HAART, which induces VS and reduced viral burden (Jaspan *et al.,* 2005), one can expect a shunt in energy usage from an activated and chronic immunological state to a state of positive nitrogen balance with an increase in both weight and height (Miller *et al.,* 2001; Majaliwa *et al*., 2009).

The paediatric ARV regimens include a double nucleoside reverse transcriptase inhibitor (NRTI) backbone with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) as the third drug (Jaspan *et al*, 2005). According to the South African ARV guidelines (DOH, 2014) and in line with the previous statement; the first line regimen for children between the ages of two and five years could consist of dual NRTIs, in this case

abacavir (ABC) and 3TC combined with either a PI, in this case lopinavir/ritonavir (LPV/r) or with NNRTI, in this case EFV (NDOH, 2015). The combination will depend on several factors, mainly the age and weight of the child, age of HAART initiation, previous combinations, intolerances and side effects, as well as resistance (Frigati *et al*., 2014; NDOH 2014). Social situations can also affect which combination is best, as poor compliance may cause worse outcomes in certain drug combinations, such as in NNRTIs (Parienti *et al*, 2004).

2.6.1 Highly active anti-retroviral therapy treatment management

Treatment with ARVs should always be initiated after proper counselling has been given to the child's primary caregiver/s and/or family. More than one session is often necessary to discuss the need for lifelong treatment and ongoing management. The extreme importance of adherence should be given special attention. A medical evaluation, including a clinical and physical examination, neurodevelopment assessment, growth assessment, full blood count (FBC), aminotransferase (ALT), VL and CD4+ % should be recorded prior to ARV initiation. TB should also be ruled out, but a work-up should not delay ARV initiation (Jaspan *et al*., 2005).

After initialising HAART, clinic visits should ideally occur monthly until compliance is demonstrated and the child is stable. Clinicians need to adjust ARV dosages at each visit according to the new weight.

Growth monitoring in the infant and child is important: weight and length/height should be recorded at each follow-up visit and head circumference should be measured in children less than two years of age in order to evaluate compliance, the caregiver is requested to bring medication along to clinic visits and to demonstrate dosages. Physical exams, laboratory monitoring and clinical judgement should be the basis of treatment options (Jaspan *et al*., 2005).

2.6.2 Highly active anti-retroviral therapy response in infants and children: influencing factors

Factors that have been identified in the literature that may influence a child's response to HAART include, and are not limited to, some of the aspects discussed in the paragraphs that follow.

Initiation age is important, especially because younger children have immature immune systems. Time of initiation of HAART plays a significant role in HIV disease progression and mortality. The WHO and South African ART guidelines recommend that HAART should be

initiated in all children younger than five years of age and fast-tracking should take place in the very young who have severe disease (WHO, 2013; NDOH, 2015). The earlier the child is initiated on HAART, the lower the risk of VF; therefore the goal posts are shifting towards even earlier diagnosis and treatment, ultimately targeting the newborn as well as the perinatally affected patient (Frigati *et al.,* 2014).

Along with age and immunity, the presence of TB may also affect the metabolism of ARV drugs, as well as virological outcomes (Frigati *et al*., 2014). The literature indicates that the risk of acquiring TB is 10% per annum in children who are co-infected with HIV, versus 10% per lifetime for their uninfected counterparts (Githinji & Jeena, 2011). Mycobacterium TB co-infection in South African children is common, with 23% of HIV-infected children presenting with TB (Frigati *et al*., 2014). Of course, poor adherence is the main reason for treatment failure. Intolerances and toxicities are also possible contributors. In the case of young children, poor adherence problems are usually related to the parent/s or caregivers (Frigati *et al*., 2014). Programme factors that may affect HAART outcomes include a lack of trained clinicians to provide HAART in poorly developed procurement or distribution systems, as well as unaffordable assays that do not aid in monitoring response to HAART treatment (Chhagan *et al*., 2008).

2.6.3 Highly active anti-retroviral therapy response on growth, body composition and the relationship with immunity

The majority of research in sub-Saharan Africa indicates that children who are initiated on HAART show consistent improvements in both WAZ and H/LAZ. Improvements in weight were rapid in the first six months, whereas improvements in length/height were more gradual (Weigel *et al.,* 2010; Sutcliffe *et al*., 2011).

Previous studies also indicate that the children with lower WAZ-scores at baseline at the time of HAART initiation had better improvements in WAZ-scores than children with higher WAZ-scores at baseline after six and 12 months of HAART, suggestive of a more robust increase in growth in more malnourished children, which is in line with other African studies (Weigel *et al*., 2010; Zanoni *et al.,* 2012; Kabue *et al*., 2008; Naidoo *et al.,* 2010). Growth differences tend to remain stable following HAART initiation, but sudden declines in weight are seen in children who develop an acute event, such as an infection (Yotebieng *et al.,* 2015). The presence of opportunistic infections and the prevalence of malnutrition, which varies by region, could have an effect on weight gain following HAART initiation (Yotebieng *et al*., 2015). It may be important to note that the length of time for catching up growth differs across cohorts. A study in Malawi found that children on ART did not reach catch-up growth after 24 months on

treatment (Weigel *et al.,* 2010) but in another Malawian study, undernourished and stunted children never reached normal WAZ and L/HAZ while on HAART (Chantry *et al.,* 2003). The same was found in a Ugandan cohort (Arpadi *et al*., 2000). Children in the United States, in contrast, reached catch-up growth after one and two years (Nachman *et al.,* 2005). A 2012 South African study described the longitudinal improvements of anthropometrical determinants after commencement of ART and found significant improvements in weight, height and mid-upper arm circumference (MUAC) z-scores among the 151 children (median baseline age = 5.1 year old), irrespective of preceding comorbidities, but stunted children did remain shorter on average after 24 months. The relationship between L/HAZ and pre-baseline comorbidities suggested that pre-baseline comorbidities (programme and/or individual) may not be entirely causative of these L/HAZ trajectories. An altered hormonal milieu was hypothesised (Chhagan *et al*., 2012). Interestingly, it was shown that nutritional interventions such as enteral and parenteral supplementation, as well as appetite stimulants to improve the nutritional status of HIV children, may improve weight gain and fat mass (not lean mass), but have only a small impact on linear growth in the short term (Miller *et al.,* 2001; Verweel *et al.,* 2002). Nutritional intervention may, however, help to strengthen the immune system, by filling nutritional gaps caused by rapid depletions seen in HIV infection.

Research has investigated the impact of HAART on body composition. Measuring body composition after HAART initiation may help to differentiate between starvation (preferential fat loss as a result of inadequate energy intake) and cachexia, referring to lean body mass (LBM) loss. Previously, data findings differed with regard to the possibility of LBM preservation in HIV-infected children on HAART (Millet *et al*., 1993; Fontana *et al*., 1999), but an increase in extremity muscle mass along with a subsequent increase in CD4+ cell has been described previously (McDermott *et al.*, 2005). A fairly recent prospective study conducted by Chantry *et al.* (2010) found a positive association between LBM and CD4%. Their methods included bioelectrical impedance and anthropometry, including skinfold measurement. The same study found no significant association between VS and increases in LBM (Chantry *et al*., 2010). The redistribution of fat mass in HIV-infected persons on HAART has been described in children and adults (Brambilla *et al.,* 2001; McDermott *et al.,* 2001). Central adiposity, with its known association with cardiovascular morbidities, is of particular concern (Verkauskiene *et al*., 2006). A positive association between higher persistent VL and fat distribution has been described, indicating that truncal fat could be related to difficulty in achieving VS (Chantry *et al.,* 2010).
Research suggests anthropometrical recovery subsequent to HAART initiation in sub-Saharan African cohorts, but with different findings related to different cohorts (Sutcliffe *et al*., 2011; Van Dijk *et al.*, 2011). These differences may be attributed to programme factors, such as successful accessibility, PMTCT and drug regimes. Individual factors like age, age at initiation, immunity and compliance will also impact results (Chhagan *et al*., 2012; Sutcliffe *et al*., 2008).

Younger children have better growth potential for catch-up than older children (>3 years). Infant and child mortality is still linked to persistent weight gain failure (Yotebieng *et al.,* 2010) and linear and ponderal growth improvements, as well as improved fat-free mass indexes, are seen when compared with population-based norms, but not when compared with HIV-exposed, uninfected counterparts. Here, study design and power may be to blame, as study design, comparing cohorts and statistical power could influence outcomes (Chantry *et al*., 2010). Certain drug regimens used per age category may also affect subsequent growth. Specific drugs have also been associated with changes in body composition, such as PIs and central adiposity, but it seems that results have not been consistent throughout (Chantry *et al.,* 2010).

2.6.4 Monitoring of highly active anti-retroviral therapy response

A primary goal of monitoring a patient initiated on HAART is to maximise the durability of first-line regimens and to prevent the development of viral resistance. Industrialised country programmes include routine measurements of plasma HIV 1-RNA (VL's) and CD4+ cell counts. Upon suspected drug resistance, genotype or phenotype resistance tests can be done in developed settings. In a resource-limited setting, this monitoring can be based only on CD4+ counts and/or clinical monitoring (Keiser *et al*., 2009). This is because the monitoring of CD4+ counts and VL is sophisticated and expensive and therefore not practical in rural settings (Yotebieng *et al*., 2010). A gap in the identification of the effectiveness of HAART exists in under-developed and developing countries and therefore, the WHO supports the use of clinical parameters, such as growth monitoring in environments where VL cannot be obtained, especially growth parameters to monitor HAART response (WHO, 2013). Weight and height trajectories may even be the only data that can be used in resource-limited settings to predict HAART response (Weigel *et al.,* 2010; Yotebieng *et al.,* 2010; Benjamin *et al.,* 2004). Certain results suggest that VL and growth associations are not independent of immune function (Hilgartner *et al*., 2001), highlighting the need to explore whether improvements are a result of immune restoration, or whether there might be another mechanism at play (Chantry *et al.,* 2010).

2.7 GROWTH ASSESSMENT AND NUTRITIONAL STATUS

Measurement of weight and height (or recumbent length) forms the basis of anthropometry in young children. Anthropometry is the science of measuring the human body in order to gain insight into body composition so that scientists can compare relative proportions under normal and abnormal conditions. Anthropometry forms part of nutritional assessment and provides a part of the puzzle needed in order to treat and manage a patient optimally. It has been

described as a “deceptively simple” tool that can be used in assessing nutritional status in individuals and communities. Anthropometry offers the advantage of objectivity and of relatively “low technology” (Duggan, 2010). It is essential that measurements are done by using a standardised technique and well calibrated equipment. Some anthropometrical techniques, such as skinfold measurements, require specialised training of personnel. Weight and height measurement are relatively easy, even for untrained personnel, as long as scales are well calibrated and height measuring equipment (stadiometer or length board) are in good, working condition (Shaw, 2015). Anthropometry forms part of the nutritional care and support of HIV infection and forms an integral part of the management of the infected child (Mawela, 2007).

2.7.1 Growth standards, references and charts explained

Growth charts are essential tools used for the evaluation of children’s health status, including their nutritional status, but the consequent decision to intervene (or not) is highly dependent on the “type” of growth chart that was used for the evaluation. This means that interpretations from growth chart evaluations will, in the end, have important implications for child health programmes (Turck *et al*., 2013).

The term “growth reference” refers simply to a tool that is used for comparison regardless of the observed differences (for example in ethnicity and socio-economic background). The term “growth standard” on the other hand, is more than a convenient scale for comparison: it implies a norm or a desirable target and is based on the understanding that the environment has a greater effect than genetics on early childhood growth, so that the growth pattern seen in optimal conditions should represent a standard (Duggan, 2010).

2.7.1.1 The World Health Organization’s growth standards (birth to five years)

The first international reference data on child growth that made use of agreed nutritional indicators and made international comparisons possible were published in 1983 (WHO, 1983). These are referred to in this study as the National Centre for Health Statistics (NCHS) or 1983 WHO reference values. In 1993, the WHO undertook a comprehensive review of the uses and interpretation of anthropometric references. The review concluded that the NCHS/WHO 1983 growth reference did not adequately represent early childhood growth, making its use as a monitoring tool for the health and nutrition of individual children, as well as population-based derivation of estimations of malnourished children, flawed.

The need for a growth standard, not a reference, was recommended by the review group (de Onis *et al.*, 2006). In response, the WHO Multicenter Growth Reference Study (MGRS) was

implemented between 1997 and 2003 to develop international growth standards for children below five years of age (WHO, 2009). The study was done to develop an international growth standard for assessing physical growth, nutritional status and motor development in all children from birth to the age of five years. More than eight thousand children from Brazil, Ghana, India, Norway, Oman and the US of America were involved in this community-based project (WHO, 2006). The infants and children who were selected for MGRS had access to proper healthcare facilities, their mothers were healthy (non-smokers) and the infants and children were fed according to recommended infant and young child feeding practices (breastfeeding and correct implementation of complementary feeding).

Growth standards prove that differences in infants and children's growth patterns (from birth to five years) are influenced by healthcare, feeding practices and nutrition, as well as environment, to a greater extent than ethnicity or genetics (WHO, 2006; Duggan, 2010). It can therefore be said that the 2006 WHO growth standards represent a "healthy" population and that malnutrition (underweight and overweight) and other weight-related conditions can be detected by using these standards (WHO, 2006).

2.7.1.2 The World Health Organization's growth references (five to 19 years)

Previously, the references (not standards) that were recommended for use by the WHO for children above five years of age were the 1977 National Centre for Health Statistics (NCHS/WHO) international growth references. Other more recent references that are used in some institutions and countries include the 2000 CDC as well as the International Obesity Task Force references (Turck *et al.,* 2013). The need to harmonise the growth assessment tools used conceptually and pragmatically was recognised and led to an evaluation by the WHO expert group in 2006. This evaluation was also motivated by the release of the previously mentioned WHO Child Growth Standards in 2006. Consequently, the WHO proceeded to reconstruct the 1977 NCHS/WHO growth references from five to 19 years (Onis *et al*., 2007). It was never feasible to follow the same methods that were used for the construction of the 2006 WHO growth standards, i.e. a multicentre study, because it would be impossible to control the dynamics of the child's environment (Onis *et al*., 2007; Turck *et al.,* 2013). Instead, it was decided that the growth references for children from five to 19 years would be constructed by using existing historical data and by applying statistical methods to smooth the data with the standards used for birth to five years old (Turck *et al.,* 2013).

In 2013, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published a discussion paper on the background and rationale of the WHO 2006 growth standards and the WHO 2007 growth references. In this discussion paper, ESPGHAN

described their development and outlined their main innovative aspects, but they also discussed limitations and made recommendations. ESPGHAN concluded that the 2006 WHO growth standards can be used as a universal tool in the assessment of growth of children, because it provides a picture of how a child will grow in an optimal environment. It provides the opportunity to assess the growth of children in relation to healthy breastfed infants worldwide and it provides a baseline for research in child growth comparison (Turck *et al*., 2013).

Regarding the WHO 2007 growth references (5-19 years), ESPGHAN concluded that national bodies must finally decide whether or not to implement these growth references because of the fact that growth patterns during the 5- to 19-year period differ between populations (Turck *et al.,* 2013). The growth of children in this age gap is influenced by ethnicity, culture, environment, socio-economic status and availability of healthy nutrients.

2.7.2 Growth monitoring in South Africa

2.7.2.1 Birth to five years

According to the available evidence, all young children should be compared with the WHO growth standards and that is why these growth standards have been included in the South African "Road to Health" (RtHB) booklets (NDOH, 2016). These A5 size booklets, colour-coded for gender, are currently in use in the South African healthcare system. The RtHBs are given to parents/caregivers when a baby is born to keep a record of valuable information of that child. In terms of monitoring of weight only, the RtHB is a practical tool, because a healthcare worker can plot the weight of the child onto the included weight-for-age chart. The RtHB also contains a length/height-for-age chart for infants and children from birth to five years of age. Electronic versions of these booklets are also available on the NDOH website (NDOH, 2016).

2.7.2.2 Children older than five years

There is no chart for children who are older than five years in the RtHB. The important question to ask is whether clinicians/healthcare workers using charts to monitor weight changes are merely noting new weights in patient files. We also need to know how weight changes of children between the ages of two and ten years old who are treated on HAART are interpreted by healthcare personnel and clinicians and at what point a change in weight (and how much weight) would indicate that intervention is needed or that treatment response is optimal.

An interesting review article from Duggan (2010) discussed the impact of the "new" WHO standards and references on the management of children in hospitals and communities in

regions with high rates of malnutrition. In preparing this review, anecdotal information regarding the use of growth charts in hospitals and clinics in some African countries, India, Pakistan, Argentina and the UK were canvassed. It was reported that the RtHBs are used, as long as they are brought to the hospitals. Growth charts for older children are seldom available. When used, the Wellcome classifications were still in use and the Waterlow percentage classification was favoured in Africa. Centile charts are still in use. Because of time constraints, raw values are also sometimes recorded instead of derived indicators, to little effect (Duggan, 2010). It would be valuable to gather more specific and up-to-date information on which charts, if any, are used across paediatric HIV clinics in South Africa.

2.7.2.3 South African Road to Health booklets

Growth charts in the South African RtHBs are used for children younger than five years (NDOH, 2016). The charts used for older children are the CDC 2000 charts. The CDC charts that are used are a revised version of the 1977 NCHS growth charts. The NCHS and the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), along with other experts, revised the charts. The charts make use of percentiles related to weight, height and body mass index (BMI) for children from two to 19 years old. The charts are a representation of the US population and the revised versions are based primarily on data collected via the National Health and Nutrition Examination Survey (NHANES). The transition between the infant charts and those for the older ages (24 to 36 months) was improved in the revised versions (Kuczmarski *et al.,* 2000). The NHANES survey conducted from 1988 to 1994, which contained more than 8 000 children aged two to six years old also led to the realisation that the number of overweight children has doubled (Kuczmarski *et al.,* 2000). Interestingly, a review by Duggan in 2010 states that the intention of (available) growth charts for school-aged children was to track risk of obesity, with little mention of risk owing to deteriorating nutritional status. Nutrition transition is a fact, but its high visibility should not obscure the other side of the spectrum, namely malnutrition in school-aged and older children related to food insecurity or secondary to illness (Duggan, 2010).

2.8 SPECIALISED GROWTH CHARTS FOR SPECIAL CHILDREN?

If the holistic management of the HIV-infected child were based on an *objective* anthropometrical assessment component of nutritional status, then the quality of life of that child would be improved (Duggan, 2010).

HIV-infected children who have been identified and initiated on HAART in South African provincial hospitals and clinics are currently being assessed and monitored by healthcare professionals in accordance with the National Consolidated Guidelines for the PMTCT of HIV and Management of HIV in Children, Adolescents and Adults document (NDOH 2014). However, it has been suggested in previous research that specialised, population specific growth norms for HIV-infected children on HAART would be much more effective in monitoring this large group of children across the globe (Yotebieng *et al*., 2015).

A change in nutritional status might warn of clinical deterioration in HIV infection (Duggan, 2010). Weight is strongly associated with HAART treatment outcomes (Yotebieng *et al*., 2010; Yotebieng *et al*., 2015). Yotebieng *et al.* (2015) explain that changes in weight are age- and sex specific. Even though the WHO growth charts are stratified according to age and sex, these growth standards and references were established using values of growing (HIV-uninfected) healthy children. The other problem with the WHO growth charts is that they start at birth, whereas HAART can be initiated at any age and it is the weight gain since HAART initiation that we are interested in, not from birth. Therefore, weight gain should ideally be plotted on specially constructed growth charts that can help the clinician, specialist, dietitian or researcher figure out how well the child is responding to HAART, especially in resource limited settings. There is no use in trying to figure out how well the child is growing when compared with other healthy children in the HAART response monitoring process.

2.8.1 New proposed age- and sex-specific weight gain norms for human immunodeficiency virus-infected children

In 2015, Yotebieng *et al.,* constructed weight gain percentile curves to investigate the association between weight gain and response to HAART in children in middle- and low-income settings. This analysis of 7,173 children from five regions over the world, including Africa and Asia, then indicated that poor weight gain was in fact not an associated factor of VS or VF.

However, the results found that weight gain below the 50th percentile was associated with an increase in mortality, regardless of the baseline characteristics of the children who were initiated on HAART (Yotebieng *et al*., 2015).

To demonstrate the possible impact of using these new recommended growth curves, we will discuss the following example: Yotebieng *et al*, (2010) found that the mean weight gain of four-year-old boys six months post-HAART initiation was 1.41 kg. If this gain in weight is plotted onto a WHO growth chart, the weight change would be interpreted as minimal. For example, a four-year-old boy weighing 11 kg, which is plotted and interpreted as <-3 WAZ score (severely underweight) at initiation of HAART, would still fall on a WAZ of <-3 after six months, after

gaining 1.41 kg. He is still severely underweight compared with children who are HIV-uninfected and growing, but the real question that should be answered is whether this child is responding to HAART. In contrast, if the same child's weight gain is plotted onto specialised growth norms (as constructed by Yotebieng *et al.,* in 2010 and 2015), the interpreter may now see an entirely different picture. The gain of 1.41 kg could move the plotted point across more than two percentiles ("line crossing"), for example, from the 10th percentile to the 75th percentile on these specially constructed curves.

Yotebieng *et al.* (2015) found that weight gain below the 33rd percentile will increase the chances of mortality two-fold. This goes to show that the above example (moving from the 10th to the 75th percentile) should actually be interpreted as "good" response to treatment (by using specialised growth norms) vs severely underweight, when compared with growing counterparts (WHO growth charts). Small losses in weight after HAART initiation can therefore set the alarm bells off much more quickly and more accurately. This underlines the fact that plotting growth onto a WHO growth chart (or CDC growth chart) is not appropriate for monitoring HAART response.

The construction of these normative curves may aid in the identification of poor response to HAART in children especially in the first year following initiation (Yotebieng *et al*., 2015). Furthermore, objective anthropometrical assessment of HIV-infected children on HAART can influence decisions and advocacy regarding nutritional supplementation for HIV-infected children (Duggan, 2010).

2.9 CONCLUSION

Without HAART, a third of infected children will not survive their first year of life, with an estimate of 30-39% mortality, and more than half will pass away before their second birthday (Newell *et al*., 2004; Meyers *et al.,* 2006). Poor growth may be a major contributor to paediatric malnutrition and morbidity (Venkatesh *et al*., 2010; Merchant & Lala, 2012) and in the HIV-infected child, impaired growth might warn of clinical deterioration in HIV infection (Duggan, 2010). However, the monitoring of weight gain should be population specific (Yotebieng *et al*., 2015), especially because HIV-infected children show a tendency to grow below the healthy standards set for age and sex (Merchant & Lala, 2012). In 2015, Yotebieng *et al*. constructed specialised weight gain norms for children on HAART. In addition, these norms are also age- and sex-specific and may serve as a useful clinical tool to monitor treatment, especially because weight gain is a sensitive indicator of treatment failure in African children on HAART (Kekitiinwa *et al.,* 2013). Objective anthropometrical assessment of HIV-infected children on HAART can influence decisions and advocacy regarding nutritional supplementation for HIV-

infected children (Duggan, 2010), or may possibly warn of the need for change in drug regimen. Weight changes can also aid as a monitoring tool for compliance with HAART.

More information regarding the growth patterns of children on HAART, especially in developing countries, is needed in order to improve the current programme and to address the epidemic that, in one way or another, affects each and every citizen of South Africa. Finally, could it be possible that the use of age- and sex-specific growth could be related to a better outcome for HIV-infected children on HAART, above and beyond merely describing their growth?

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CHAPTER 3: METHODOLOGY

3.1 INTRODUCTION

A detailed description of the methods used to complete this study is given in this section, with only a concise summary in the article.

3.2 STUDY DESIGN AND SETTING

This project was approached in a quantitative, descriptive-comparative manner with a retrospective design. Patient records, progress notes and blood results that form part of the filing system of the Dr George Mukhari Academic Hospital's (DGMAH) paediatric anti-retroviral (ARV) clinic were accessed between February 2017 and June 2017. Weight and length/height of the study population were recorded. Other parameters, such as highly active anti-retroviral therapy (HAART) regimens and routine blood work, along with clinical and immunological signs and markers that were measured and recorded in patient files, were also collected.

DGMAH is situated in Ga-Rankuwa in the North-West region of the Gauteng province, South Africa. DGMAH has a total of 1 652 approved beds and the catchment area population is 1.2 million (Census, 2011). DGMAH also serves as a training institution for medical interns and students from Sefako Makgatho Health Sciences University (SMU). This research project was conducted in the paediatric out-patient department (POPD). The POPD runs an ARV clinic every Tuesday of the week and keeps a separate filing system for patients that are initiated on HAART. The POPD has an emergency room, nurse's reception area with kitchen, restrooms and an office and also various consultation rooms. The area at the back of the POPD is the filing room and office of data capturers.

The researcher had ethical approvals that permitted her to access this ARV clinic's filing cabinet. The patient files contain information of the children that have been initiated on HAART and who attend follow-up visits at this ARV clinic on a Tuesday to see a medical doctor or intern. The medical doctor would have done a full assessment of a child who requires HAART or a child who has been given a follow-up appointment after HAART initiation. Progress notes are written in order to see how the child is performing on the HAART in terms of certain anthropometrical measurements and clinical signs. Blood results are also kept in the files and HAART is recorded at each visit.

3.3 STUDY SUBJECTS

3.3.1 Population

Boys and girls aged between birth and 120 months/ten years old who were initiated on HAART at any time during the lifespan of this ARV clinic and who attended follow-up visits at the ARV clinic of DGMAH for a minimum of six months and a maximum of 24 months following HAART initiation were eligible for inclusion in this research project.

3.3.2 Data selection and collection

The ARV clinic had a filing room with a large cabinet that contained the files of all the "active" members that attended. This means that if ever a child was initiated on HAART by the clinic, a file was opened for the child and that file received a number and was then filed in that cabinet. The numbering was done as new patients were initiated on HAART, not in any other order (e.g. not alphabetical or by date of birth). The cabinet contained "active files" which, by definition of the ARV managing nurse, included a file for every child initiated on HAART, whether the child was alive or not. The only time that a child's file would be removed from this cabinet would be if the child was reported as deceased with a valid death certificate (reporting was apparently rarely done, however), or if a child was transferred to another clinic because of proximity. Children older than 15 years of age who were still alive and on treatment were transferred with their patient files to the adult ARV clinic on the same hospital premises. In essence, this active filing cabinet would then consist of the patient files of children who had been initiated on HAART (whether alive or not), were younger than 15 years and who were still treated at this clinic, as well as those of the children who had been lost to treatment. A number given to a patient file would not be repeated. Numbering started from 1 to >2 500 in this cabinet, with not all numbers present, for the reasons mentioned. The managing nurse estimated that there would be around 2 000 "active files" during the time of data collection.

Owing to the random filing technique used at the clinic, the researcher could make use of a convenience sampling method. Files were screened for eligibility by checking, firstly, the age of the child and secondly, whether there were enough data available. Screening also involved checking the duration of tuberculosis (TB) medication during the first 24 months following HAART initiation. More screening criteria are discussed in the following section covering inclusion and exclusion criteria.

3.3.3 Inclusion and exclusion criteria

Children of both sexes from birth to ten years of age who had been initiated on HAART were eligible for inclusion in the study. The data captured were required not to be parallel to an age older than 120 months/ten years, because the centile curves by Yotebieng *et al*. (2015) are limited to data for children younger than 120 months.

Children who had received TB treatment for longer than six months during the first two years after HAART initiation were excluded because of the impact of chronic TB on weight, as well as the interaction of TB medication with HAART. TB infection is usually treated with rifampicin, which affects the metabolism of ARV drugs as well as virological outcomes (Frigati *et al*., 2014), especially lopinavir/ritonavir (LPV/r), which is part of one of the first line-regimen combinations for children in South Africa (NDOH, 2015). This may also have a direct impact on the growth of the child, as TB is also associated with immune reconstitution inflammatory syndrome (IRIS). IRIS is a major complication of HAART initiation and presents as an exacerbation of opportunistic infections associated with immune recovery within six months of starting the treatment (Smith *et al.,* 2009).

The child should have a baseline weight reading (at initiation) and then at least one follow-up weight reading falling on a date in the 6^{th}, 12^{th}, 18^{th} or 24^{th} month post-HAART initiation. Weight readings that fell half a month short of or over these dates were rounded off and still accepted.

3.4 DATA COLLECTION

The researcher made appointments to use a vacant consultation room directly next to the filing room in the POPD to do data capturing alone, without disturbing any patient consultations. The researcher started working through the patient files from one side of the filing cabinet, screening, including, excluding and working her way through the files, until the planned sample size of approximately 100 files was reached. It became apparent that the first/earlier screened files were of children who were initiated on HAART in 2004, which was when the National ARV Programme was rolled out in South Africa (NDOH, 2004).

3.4.1 Data collection spread sheet

All the data were transferred onto an electronic Microsoft Excel spread sheet. The data that the researcher was interested in will be described in terms of how such data fit into the research methodology.

3.4.1.1 Demographic information

Data were captured anonymously and no personal data, such as address or telephone number or details of caregivers, were captured. Dates of birth were captured in order to calculate initiation and follow-up ages. This will be discussed in the data analysis section 3.6. Dates of birth were also required in order to calculate the weight-for-age z-scores (WAZ) and the length/height-for-age z-scores (L/HAZ) statistically – refer to section 3.7. The datasheet that contained birth dates was shared only among researchers. Demographic data that was recorded included gender, age and date of birth.

3.4.1.2 Highly active anti-retroviral therapy regimen

The HAART regimen was captured for every follow-up visit. If a change was made to any drug given, it was indicated at what stage of the follow-up visit it was made. The new type of drug was also indicated. The recording of the HAART drugs could be done very accurately because information regarding the HAART regimen was recorded in detail in the patient files.

3.4.1.3 Clinical and/or immunological staging of human immunodeficiency virus infection

Progress notes were read in order to see where the child was in terms of clinical and/or immunological staging. In general, it was found that not all clinicians recorded the clinical stage that the child presented with, but where it had been written in the patient file, it was captured by the researcher. Clinical staging guidelines used by clinicians include those of the World Health Organization (WHO) staging (WHO, 2006; WHO, 2007), which was discussed in Chapter 2.

3.4.1.4 Biochemistry

Biochemical data collected included T-lymphocyte-bearing CD4 receptor (CD4+) percentage (%) and serum haemoglobin (Hb) levels, measured in g/dL. These blood values were recorded based on information from previous studies. Even though their exploration will not form part of the primary objectives of the research, it will help to provide a richer research milieu. An example includes that of unexplained anaemia (Hb value < 8g/dL), which has been observed in the human immunodeficiency virus (HIV)-infected paediatric population and which forms part of the WHO's clinical category 3 (WHO, 2006; WHO, 2007). Although anaemia can be related to nutritional intakes of the micronutrient, that is, iron found in animal and plant proteins, other causes of anaemia include chronic diseases, opportunistic infections, and deficient erythropoiesis, which is common in the HIV-infected paediatric population (Calis *et al.,* 2008; Semba & Gray, 2001; Totin *et al.,* 2002). A South African study conducted by Kruger *et al*.

(2013) pointed out that African prevalence data regarding anaemia in children 3-14 years were lacking and this study could provide a piece of the puzzle owing to routine Hb monitoring in the ARV clinic.

Information on CD4+ cells is important because of its possible significance when associations are investigated between the infant or child's immunity and growth pattern after different stages following HAART initiation. A better picture in terms of the association between growth and HAART response, linked to CD4+ cell % changes, may provide more information on the significance of growth (weight gain and length/height gain) monitoring as a component of treatment success.

3.4.1.5 Anthropometrical measurements

Patient files contained an ARV flowchart which had spaces where doctors could record ARVs, dosages of ARVs and other related medication, such as cotrimoxazole, multivitamins or vitamin B-complex, and weight for each visit.

Weight at each visit was the outcome variable in this study, as we wanted to compare one cohort with newly suggested norms. Seca354™ digital weight scales (Hamburg, Germany) were used for routine weight measurements, in kilograms (kg) of young children that were unable to stand due to ill health. MICRO™ electronic floor scales (Optima Electronics, George, South Africa) were used for routine weight measurements of children that were able to stand. Weight measurements were recorded to the nearest two decimals on the ARV flowchart and mostly also in the patient files. Unfortunately, we could not do post hoc calibration of the scales for weights recorded earlier, but scales currently in use were calibrated using calibration weights of 10kg to get an estimation of the accuracy of the scales used in the clinic; the calibration result will be reported with the results of the study.

Recumbent length and height measurements were also captured and were written in the patient files. Length/height measurements were not always recorded as routinely as weight. The researcher also noticed that height measurements were recorded more frequently after initiation of HAART, but not followed up during later stages. Standard measuring tapes and Kabi Vitrum™ stadiometers (United States) were used when measuring the length/height of the child.

3.4.1.6 Tuberculosis co-infection

A child was eligible for inclusion if he/she was treated for TB co-infection for ≤ six months during HAART. TB treatment was recorded on the ARV flowchart along with the duration of the

treatment. If TB treatment was given, it was usually for six months at a time. The researcher captured those subjects who received TB treatment for the maximum (research inclusion) duration of six months during the course of HAART.

3.5 ETHICAL CONSIDERATIONS

All data capturing from the files was conducted by the researcher (J. Scholtz) in the clinic and information was captured anonymously on a password-protected laptop. Data were not discussed with any person beyond the research team. One Microsoft Excel datasheet contained only participant number, date of birth, date of measurement, height and weight. This datasheet was retained only for calculation of age at follow-up periods and WAZ and L/HAZ and was deleted after calculations and when the relevant data were carried over to the complete ethical dataset. The final datasheet did not present birth dates, so that no child could be identified from the dataset. Ethical approval was obtained from the North-West University Research and Ethics Committee (HREC) (NWU ethics number: NWU-00080-16-A1) (Addendum A). Permission to conduct research at the POPD was also given by the Chief Executive Official of DGMAH (Addendum C) and ethical clearance from the Sefako Makgatho Health Sciences University Ethics Committee (SMUREC) (Addendum B), prior to HREC approval. This project was conducted under strictly controlled ethical conditions at all times, in accordance with the World Medical Association Declaration of Helsinki.

3.6 DATA ANALYSES

The researcher calculated the HAART initiation age (from the date of birth). This calculation was done by hand, using an online age calculator. Microsoft Excel was used to calculate age at follow-up and weight gain at each follow-up. Each weight gain was plotted onto the appropriate growth curve constructed by Yotebieng *et al*. (2015). These age-specific percentile curves are specified for weight gain after HAART initiation at 6 months, 12 months, 18 months and 24 months follow-up “ages”. Weight gain (in kg) on the y-axis and current age (in months) on the x-axis were plotted manually, after which the percentile or percentile range for that specific plotting point was captured. Percentiles ranged from the 5^{th}, 10^{th}, 25^{th}, 33^{rd}, 50^{th}, 75^{th} and 90^{th} to the 97^{th} percentile. Percentiles and percentile ranges were coded in the following manner: 1: <3 percentile, 2: 3^{rd} to 9^{th} percentile, 3: 10^{th} to 24^{th} percentile, 4: 25^{th} to 32^{nd} percentile, 5: 33^{rd} to 49^{th} percentile, 6: 50^{th} to 74^{th} percentile, 7: 75^{th} to 89^{th} percentile, 8: 90^{th} to 97^{th} percentile and 9: >97^{th} percentile. After coding, the researcher could interpret the growth pattern for each individual child. Interpretations of growth patterns were categorised in the following manner: 1 = decrease, 2 = maintain, 3 = increase and 4 = fluctuate.

3.7 STATISTICAL ANALYSES

Data were checked for outliers and routinely corrected during data collection by confirming the values of every 5th file according to the original data in the files. New variables were created for total weight gain over 6- and 12 months (and if available, 18 and 24 months) by subtracting baseline weight from weight at 6, 12, 18 and 24 months' follow-up, respectively, to assess the weight changes of children from initiation of HAART to follow-up. The WAZ were plotted on the usual WHO growth chart for healthy girls and boys, and weight gains for age were plotted on the newly suggested weight gain charts for HIV-positive children (6, 12, 18 and 24 months' follow-up).

Descriptive statistics were used to describe the baseline and follow-up characteristics of the boys and girls. The distribution of all continuous variables was tested by using histograms, Q-Q plots and the Shapiro-Wilk test. The variables of the study participants are presented as means and standard deviations (normally distributed data) or medians and inter-quartile range (for data not normally distributed). Categorical data (sex, HAART regimen, TB medication) are presented as frequencies. Statistical significance was set at a p-value of < 0.05. Mixed model analysis was also used to test for significance of increases in weight, WAZ, Hb and CD4+%. Mixed model analysis of longitudinal data was performed using the restricted maximum likelihood (REML) function with an unstructured covariance type. The quality of fit was estimated by Akaike's information criterion (AIC). Repeated comparisons were done to test for changes between 6-monthly follow-up visits, with Sidak adjustment for multiple comparisons. A Kappa test for agreement between categories was performed to evaluate and compare mean differences of individual weight changes at each 6-monthly follow-up visit. The categories that were compared were the weight gain patterns of the children according to the usual WHO growth charts versus those of the newly proposed weight gain percentiles, specifically designed for children who are treated with ARVs, as stipulated by Yotebieng *et al.* (2015). A subgroup analysis (Kappa test) was done, where only children with a low weight at HAART initiation were included, as defined by WHO standards of WAZ-score < -1. Mean differences were calculated between mean weight change by age category at the 24-month follow-up visit and the age-specific and sex-specific weight gain norms (Yotebieng *et al.,* 2015). The range of deviations from the norms is presented and the effect sizes of the differences were calculated as mean difference divided by standard deviation of the mean weight gain at 24-month follow-up for each age group of boys and girls. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 24 (IBM Company, Armonk, NY, USA).

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CHAPTER 4: ARTICLE

This article is intended for submission to the journal: **'Southern African Journal of HIV Medicine'**

Author guidelines for the relevant journal are found in Addendum E.

Research Paper

Comparison of weight gain to age- and sex-specific norms in children 2 to 10 years old on highly active anti-retroviral treatment

J. Scholtz, H.S. Kruger, S. Ellis

Centre of Excellence for Nutrition, North-West University, Potchefstroom Campus, Potchefstroom, South Africa

Statistics Consultation Department, North-West University, Potchefstroom Campus, Potchefstroom, South Africa

Correspondence: Prof. H.S Kruger

Box 594

Centre of Excellence for Nutrition

North-West University, Potchefstroom Campus,

Potchefstroom

South Africa, 2520

Telephone Office: +27182992482

e-mail: Salome.Kruger@nwu.ac.za

Key terms: HIV, infants, children, weight, height, HAART, growth charts, WAZ, catch-up growth, WHO stage, Hb, CD4+%

Abstract

Background:

Inadequate weight gain might warn of clinical deterioration in children infected by human immunodeficiency virus (HIV), but existing references for weight gain in children initiated on highly active antiretroviral therapy (HAART) at different ages are not being implemented.

Objectives:

The objectives of this study were to assess weight gain and weight gain patterns of infants/children initiated on HAART. Furthermore, comparisons between the interpretations of weight gain were made from two references: the World Health Organisation's (WHO) weight-for-age z-scores (WAZ) and the sex- and age-specific norms that have been constructed from data of HIV-infected infants/children on HAART.

Methods:

This project was approached in a quantitative, descriptive-comparative manner with a retrospective design. Weight and other data relating to HIV were captured from patient records kept from the time that an infant/child was initiated on HAART. The weight gain recorded of the 98 children < ten years old during the 24 months following HAART initiation was assessed and analysed.

Results:

Rate of weight and length gain improved significantly over the 24 months from the time that HAART was initiated, but complete catch-up growth was not reached. The interpretations of weight gain patterns varied significantly between the two reference charts that were used: according to the WHO charts, 69% of the children had an increase in rate of weight gain versus only 16% according to the age- and sex-specific weight gain charts.

Conclusion:

The use of HIV weight gain charts is a simple, low cost clinical tool that can aid in the monitoring of HAART response in children.

Introduction

Weight gain in children is associated with HAART treatment outcomes[1] and the need for population-specific growth curves for the monitoring of HIV-infected children on HAART has been established[2].

HIV and acquired immunodeficiency syndrome (AIDS) is an epidemic that affects 36.7 million people globally, of which 2.1 million are children younger than 15 years old. Of the known infected population, 46.3% is treated with HAART. Eastern and southern Africa remains the world's most burdened region, with South Africa carrying the largest epidemic. An estimated 7.1 million South African's were living with HIV during middle 2017 (UNAIDS, 2017)[3]. The South African National HAART Programme is the largest of its kind globally[4], with all HIV-exposed infants and children less than five years of age being eligible for HAART, irrespective of their T-lymphocyte-bearing CD4 receptor (CD4+) count[5]. Without HAART, a third of infected children will not survive their first year of life, with an estimate of a 30-39% mortality rate and more than half of HIV-infected children that could die before their second birthday.[6,7]

Poor growth, which is associated with HIV progression, may be a major contributor to paediatric malnutrition and morbidity.[8,9] The literature suggests that poor weight gain as a measure of nutritional status might warn of deterioration in HIV infection.[10] In 2015, Yotebieng et al.[1] constructed weight gain percentile curves for children placed on HAART. These sex- and age specific weight gain norms may be a useful clinical tool, as weight gain is a sensitive indicator of treatment failure in African children on anti-retroviral treatment (ART).[11]

Population-, age- and sex-specific weight gain norms for the objective growth monitoring of HIV infected children on HAART may impact on decisions at national level and on advocacy regarding nutritional supplementation in the future[10]. Poor weight gain could also provide the health care professional with a clinical tool to monitor ART[11], and possibly to monitor compliance to therapy.

The objectives of the study were to assess and analyse the weight gain and weight gain patterns of children younger than ten years old, from initiation of HAART to 6, 12, 18 and 24 months' follow-up after HAART initiation. This study also compares the interpretations of weight gain patterns of the same group of children according to two different weight monitoring reference charts: age- and sex-specific HIV charts, proposed by Yotebieng et al.[1] and weight pattern interpretations according to current WHO weight-for-age z-scores (WAZ).[12,13]

This study serves as a logical extension of the work done by Yotebieng and co-workers[1], who created age- and sex-specific HIV charts to monitor weight gain in children initiated on HAART.

These normative percentile curves were constructed and Cox proportional models were used to assess the association between lower percentiles (<50th) of weight gain distribution at different time points and subsequent virological suppression, virological failure and subsequent death[1]. In addition, this study will provide valuable information on the weight gain patterns of children below the age of ten years who have been initiated on HAART. Weight gain pattern data, especially in developing countries, are needed in order to improve current monitoring programmes.

Methods

Study design

This project was approached in a quantitative, descriptive-comparative manner with a retrospective design. Patient records were accessed to collect weight and length/height changes of the boys and girls that received HAART from an antiretroviral (ARV) clinic in Gauteng, South Africa. Other parameters, such as HAART regimen and routine blood biochemistry, along with clinical and immunological signs and markers that were measured and entered in patient files, were also recorded.

Study subjects

Boys and girls aged between birth and 120 months/ten years, who were initiated on HAART at any time during the lifespan of this ARV clinic and who attended follow-up visits for a minimum of six months and a maximum of 24 months after HAART was started, were eligible for inclusion in this research project. Infants/children were excluded if they had received tuberculosis (TB) treatment for more than six months during the first 24 months after initiation of HAART.

Data selection and collection

The ARV clinic's filing cabinet contained the patient records of the 'active' infants/children (n ~ 2 000) who were initiated on HAART (both alive or not), aged younger than 15 years. This includes those who are still treated at this clinic, as well as those who have been lost to follow-up. Owing to the random filing technique that made it difficult to access files according to age or follow-up time, a convenience sampling method was used to locate the files of eligible children until the planned sample size of approximately 100 files was reached. The files were

selected as they were filed (numerically) and selection started from the time that the clinic started in 2004, until the sample size was reached.

All the data were captured electronically on a Microsoft Excel spreadsheet. Dates of birth were captured in order to calculate initiation and follow-up ages, as well as WAZ and length/height-for-age z-score (L/HAZ). Demographic data included sex, age and date of birth and HAART regimen was recorded for every follow-up visit. Progress notes included clinical and/or immunological staging, and biochemical data collected included CD4+ percentage (%) and serum haemoglobin (Hb) levels. These results will not form part of the primary objectives of the research, but will help to create a richer research milieu.

Weight at each visit was recorded to assess the weight gain patterns of the children, the primary outcome variable in this study. In addition, we compared the weight gain pattern interpretations between the WHO growth charts[12,13] and the suggested age- and sex-specific weight gain charts.[1] Length/height measurements were also captured if recorded in the patient files.

Data analysis

We analysed the data of the infants/children with a recorded baseline weight (at initiation of HAART) and at least one follow-up visit that fell on a date that was either on the 6^{th}, 12^{th}, 18^{th} or 24^{th} month post-HAART initiation. Weight records that fell half a month before or after these follow-up dates were rounded off and accepted. The researcher calculated the HAART initiation age (from the date of birth), by using an online age calculator. Microsoft Excel was used to calculate age at follow-up and weight gain for each follow-up. Each weight gain was plotted onto the appropriate growth curve.[1] These age-specific percentile curves are specified for weight gain after HAART initiation, then at 6-month, 12-month, 18-month and 24-month follow-ups. Weight gain (in kg) on the y-axis against current age (in months) on the x-axis was plotted manually, after which the percentile or percentile range for that specific plotting point was captured. Percentiles ranged from the 5^{th}, 10^{th}, 25^{th}, 33^{rd}, 50^{th}, 75^{th} and 90^{th} to the 97^{th} percentile. Percentiles and percentile ranges were coded in the following manner: 1: <3 percentile, 2: 3^{rd} to 9^{th} percentile, 3: 10^{th} to 24^{th} percentile, 4: 25^{th} to 32rd percentile, 5: 33^{rd} to 49^{th} percentile, 6: 50^{th} to 74^{th} percentile, 7: 75^{th} to 89^{th} percentile, 8: 90^{th} to 97^{th} percentile and 9: >97^{th} percentile. After coding, the researcher could interpret the growth pattern for each individual child. Interpretations of growth patterns were categorised in the following manner: 1 = decrease (consistent decrease from high to lower percentiles), 2 = maintain (at least 3 out of 4 weight gains were in the same percentile range), 3 = increase (consistent increase from low to higher percentiles) and 4 = fluctuate (no consistent pattern of increase, decrease or maintenance).

Validity

The scales that are used in the ARV clinic where we conducted the study were calibrated using a calibration weight to confirm the validity of the recorded weights. The scales were calibrated and the weight differences ranged between 0 and 0.2 kg, indicating a 98% accuracy of measurement. This calibration was done during the time of data collection and my therefore not display the calibration values as they were during the actual measurements.

Statistical analyses

Data were checked for outliers and routinely corrected during data collection by confirming the values of every 5th file according to the original data in the files. Total weight gain over 6- and 12 months (and if available, 18 and 24 months) was calculated and plotted on the usual WHO growth chart for healthy children currently used in paediatric clinics in South Africa, as well as on the suggested weight gain chart for HIV-positive children.[1]

Descriptive statistics were used to describe the baseline and follow-up characteristics of the boys and girls. The distribution of all continuous variables was tested by using histograms, Q-Q plots and the Shapiro-Wilk test. The variables of the study participants are presented as means and standard deviations (normally distributed data) or medians and inter-quartile range (for data not normally distributed). Categorical data (sex, HAART regimen, WHO stage) are presented as frequencies. A p-value of < 0.05 was deemed to be statistically significant.

Mixed model analysis also used to test for significance of increases in weight, WAZ, Hb and CD4%. Mixed methods analysis of longitudinal data was performed, using the restricted maximum likelihood (REML) function with an unstructured covariance type. The quality of fit was estimated by Akaike's information criterion (AIC). Repeated comparisons were made to test for changes between 6-monthly follow-up visits, with Sidak adjustment for multiple comparisons. A Kappa test for agreement between the four identified growth pattern categories according to the two growth norms was performed. The Kappa test was also repeated in a subgroup analysis, where only children with a low weight at HAART initiation were included, as defined by WAZ-score < -1. The range of deviations from the norms is presented and the effect sizes of the differences were calculated as mean difference divided by standard deviation of the mean weight gain at 24-month follow-up for each age group of boys and girls. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 24 (IBM Company, Armonk, NY, USA).

Ethical considerations

All information was collected from patient records only. No informed consent was sought from the parents of the children. All the data were captured anonymously on a password-protected laptop. Ethical approval was obtained by the North-West University Research and Ethics Committee (HREC) (NWU ethics number: NWU-00080-16-A1) (Addendum A). Permission to conduct research at the clinic was also given by the Chief Executive Official of the hospital (Addendum C) and ethical clearance of the Sefako Makgatho Health Sciences University Ethics Committee (SMUREC) (Addendum B), prior to HREC approval. This project was conducted under strictly controlled ethical conditions at all times, in accordance with the World Medical Association Declaration of Helsinki.

Results

The data screening for inclusion eligibility and exclusions is shown in Table 1. The total number of baseline and follow-up data points that formed part of the statistical analyses was N = 363, which was derived from 98 infants/children. Most of the exclusions were made as a result of missing information of infants/children who had been transferred out of this clinic, as well as infants/children whose weight gain data fell too far outside of the specified 6, 12, 18 and 24 months' follow-up periods. In addition, if any important data or a part of the patient's file were reported missing, the file was not used for data collection. A total of 94 files were excluded from this research, while 98 files were included for analyses.

TABLE 1: Data screening, eligible data points and subjects

Inclusions			**Exclusions**	
Baseline and follow-up data	**Children**	**Data points**	**Criteria**	**Count**
Baseline and 1 follow-up	12	24	▪ Age > 10 years	19
Baseline and 2 follow-up visits	27	81	▪ TB > 6 months	5
Baseline and 3 follow-up visits	37	148	▪ No baseline weight	3
Baseline and 4 follow-up visits	22	110	▪ Missing information	61
			▪ Poor HAART compliance (according to clinical notes)	6
Total	***n*=98**	***N*=363**		**94**

a) B=baseline; FU=follow-up; *n*=number of subjects; *N*=number of data points

The infants/children included in the study were classified according to the WHO clinical staging of HIV/AIDS for children with confirmed HIV infection[14], as shown in Figure 1.

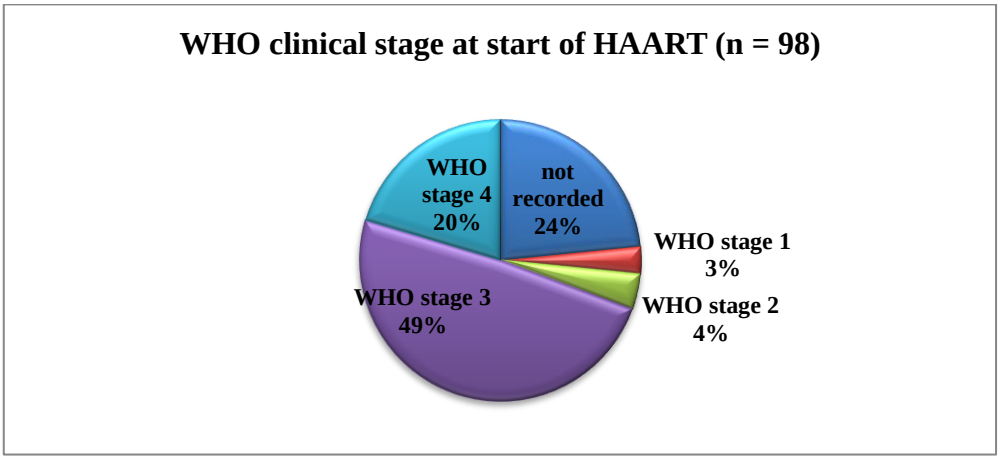

FIGURE 1: Staging of the infants/children included in the study according to WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

It was calculated that the HAART regimen of a total of 14% of the infants/children was changed at some point during the 24-month follow-up period, indicating that 86% of the infants/children remained on the same ARV regime for the study period of 24 months.

Table 2 displays the baseline and follow-up characteristics of the boys and girls. Girls were significantly older than boys at HAART initiation (42.2- versus 30 months old). Weight increased significantly from HAART initiation to 24 months and also at each of the 6-month intervals compared with baseline ($p < 0.0001$; AIC = 1 484.9). L/HAZ did not increase significantly from HAART initiation to 6 months' follow-up ($p = 0.058$), but increased significantly from baseline to 12, 18 and 24 months compared with baseline ($p \leq 0.001$; AIC = 895.3). The mean WAZ curve started from a z-score of < -2.1 which is in the underweight range for age. The biggest mean improvements were at the 12- and 18-month follow-up periods, with a change from WAZ = -2.1 to WAZ = -1. WAZ increased significantly from HAART initiation to 24 months and also at each follow-up visit compared with baseline ($p < 0.0001$; AIC = 970.3). Both Hb and CD4 % increased significantly from HAART initiation to 24 months and also between each follow-up visit compared with baseline ($p<0.0001$; AIC = 723.1 and AIC = 1 655.3, respectively.

TABLE 2: Characteristics of the study population

	All children			Boys			Girls			
	N	**Mean**	**SD**	***N***	**Mean**	**SD**	***N***	**Mean**	**SD**	**P**
Initiation age (months)	98	35.5	27.6	54	30	24.9	44	42.4	29.3	0.03*
Weight at initiation (kg)	98	10.8	4.5	54	10.3	4.2	44	11.5	4.8	0.18
WAZ at initiation	97	-2.1	1.5	48	-2	1.6	31	-2.3	1.6	0.37
WAZ at 6 m FU	58	-1.3	1.1	24	-1.4	1.1	20	-1	1.4	0.31
WAZ at 12 m FU	58	-1	1	29	-1	1.0	16	-0.9	1.3	0.90
WAZ at 18 m FU	79	-1	0.8	35	-0.9	0.9	18	-1	1	0.78
WAZ at 24 m FU	70	-1.1	0.9	25	-1.1	0.9	17	-1	1.2	0.74
L/HAZ at initiation	92	-2.3	1.26	51	-2.3	1.3	41	-2.2	1.2	0.71
CD4+ (%)	73	15	8.8	37	14.7	8.9	36	15.8	8.7	0.58
Hb (g/dL)	68	9.7	1.4	38	9.7	1.4	30	9.7	1.4	0.84

a) *n*=number of subjects; m=mean; SD=standard deviation; FU=follow-up
b) *=statistically significant p value
c) WAZ and HAZ is classified according to WHO growth standards[12] for children from birth to 5 years

A further analysis of the baseline characteristics of the children is presented in Table 3, which indicates that there were no significant differences in the prevalence of malnutrition at initiation of HAART between the boys and girls. The mean L/HAZ score at initiation was -2.3, with 56.5% of the population being stunted when HAART was started.

TABLE 3: Differences in prevalence of malnutrition at initiation of HAART between boys and girls

	All children (n=98)		Boys (n=54)		Girls (n=44)		P*
	N	**%**	***N***	**%**	***N***	**%**	
Underweight at initiation	52	53.1	28	51.8	24	54.5	0.43
Stunted at initiation (L/HAZ <-2)	52	56.5	29	60.4	23	56.1	0.68

a) *n*=number of subjects
b) 'Underweight' and 'stunted' were classified according to WHO growth standards[12]
c) *Level of significance, comparison with chi-square test
d) Height measurements were available for 92 children

Figure 2 depicts the agreement between categories of weight gain patterns according to two different references: HIV weight gain charts[1] versus WHO growth charts.[12,13] In Figure 2, the number of subjects (*n* = 86) includes those infants/children who had at least two follow-up visits

after HAART initiation. According to the HIV weight gain charts,[1] most (62.8%) of the infants/children remained within the same percentile range of weight gain (maintain) for their sex and follow-up time, while the rate of weight gain of 16.3% of the infants/children had decreased across percentiles. The same proportion of infants/children showed an increase in rate of weight gain (16.3%), while only 4.6% showed fluctuating weight gain patterns. This is an indication that almost two-thirds of the children gained weight satisfactorily, when assessed using age, sex and HIV-specific growth charts.

Interpretation of age-specific weight gain patterns according to WAZ-scores (WHO)[12,13] shows that most of the infant's/children's weight gain (68.9%) increased from a lower to a higher percentile. Only 10.5% of infant's/children's rate of weight gain had decreased from a higher to a lower percentile, which is just over half of the number of infants/children that maintained their weight gain pattern (19.8%). Only 1.2% of the infants/children showed a pattern of fluctuating weight gain.

Finally, Figure 2 shows that there was poor agreement between categories of weight gain patterns as assessed by HIV weight gain charts[4] versus WHO growth charts based on WAZ[12,13] (Kappa value = 0.003, p = 0.95).

Afterwards, a subgroup analysis that included only the infants/children who had a low weight at initiation of HAART (n = 51, WAZ of < -1) was done. Figure 3 shows the result of the subgroup comparison. There was an improvement in the agreement between the weight gain patterns of the two weight gain charts (HIV weight gain charts[1] versus WHO growth charts[12,13]), but the agreement was, however, still not statistically significant (Kappa value = 0.03; p = 0.58).

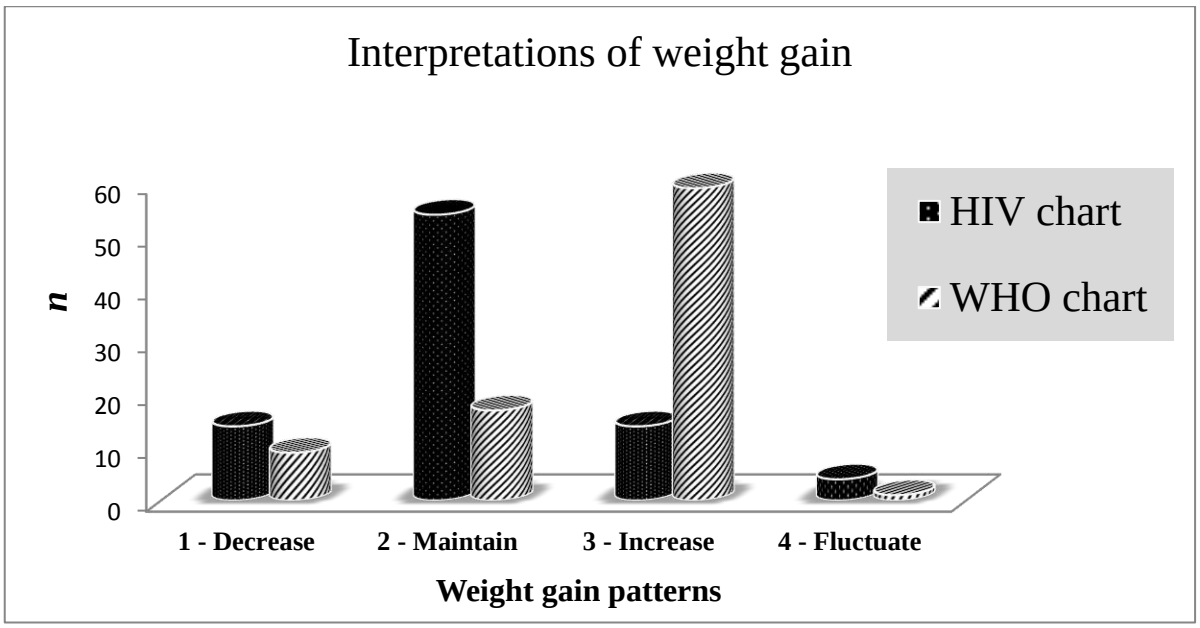

FIGURE 2: Weight gain patterns according to two references: interpretation according to HIV weight gain charts[1] versus WAZ- scores (WHO charts)[12,13]

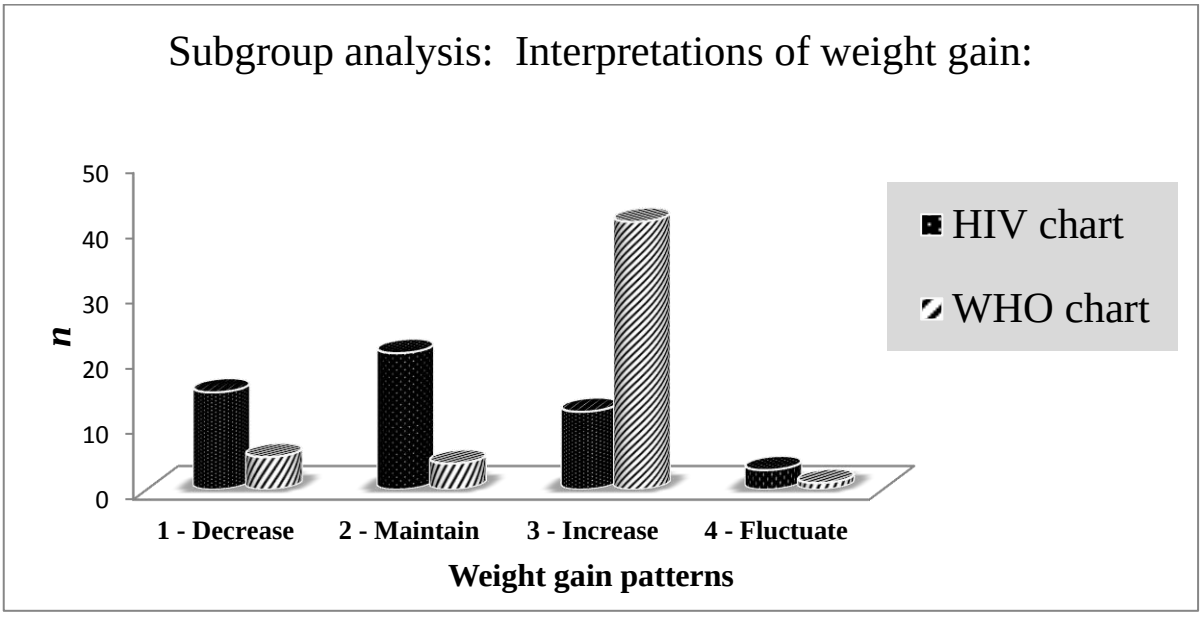

FIGURE 3: Subgroup analysis of infants/children with low baseline weight at HAART initiation; weight gain patterns according to two references: interpretation according to HIV weight gain charts[1] versus WAZ- scores (WHO charts)[12,13]

Mean differences between weight change by age category at the 24-month follow-up visit and the age- and sex-specific weight gain norms[1] are shown in Table 4. The range of deviations from the norms is presented and the effect sizes of the differences were calculated as mean difference

divided by standard deviation of the mean differences at 24-month follow-up for each age group of boys and girls.

TABLE 4: Differences between mean weight change by age category of the boys and girls at the 24-month follow-up visit and the age-specific and sex-specific weight gain norms

Age group (months)	N	Actual weight gain at 24 months (kg)	Proposed weight gain at 24 months (kg)*	Weight gain range (kg)	Mean difference between proposed and actual weight gain (kg)	Effect size (mean diff / SD)
		Mean ± SD	50th percentile			
Boys						
< 40	14	4.87 ± 1.32	5.20	2.8-7.5	-0.33	0.25
40-59	9	5.04 ± 1.31	4.80	2.9-7.2	0.24	0.18
60-79	14	5.60 ±2.08	4.4	2.1-9	1.20	0.58
80-99	0	-	-	-	-	-
100-120	2	5.45 ± 1.62	5.0	4.3-6.6	0.45	0.28
			Girls			
< 40	8	5.68 ± 1.69	5.0	3.1-8.4	0.68	0.40
40-59	9	5.48 ± 1.99	4.5	2.7-8.7	0.98	0.49
60-79	8	5.04 ±1.27	4.2	2.6-7.5	0.84	0.66
80-99	0	-	-	-	-	-
100-120	6	4.75 ± 1.31	5.0	2.6-6.1	-0.25	0.19

SD = standard deviation

*Proposed median weight gain according to the weight gain charts for HIV positive children[1]

Discussion

Outline of the results

The objective of this study was to assess and analyse the weight gain and weight gain patterns of infants/children younger than ten years old from the time of HAART initiation to 6, 12, 18 and 24 months follow-up visits. More than half of the children in this study were underweight and stunted for their age when they started HAART, according to the WHO's growth standards and references.[12,13] These findings are in line with those of the literature, describing the association between growth and HIV infection[9] and the tendency of HIV-infected infants to be stunted by as early as 3 months of life.[8] On average, the boys were 30 months and the girls 42.2 months old when HAART was initiated. This is still not early enough, especially because research suggests that children should be initiated early, aiming for perinatal and newborn age at initiation of HAART in order to lower the risk of virological failure.[14]

Most of the infants/children in this study were reported to be clinically in Stage 3 and Stage 4 of HIV infection (69%), indicating advanced HIV disease progression.[15] Research suggests that children with advanced disease progression and associated poor growth at HAART initiation may show larger improvements in WAZ-scores when compared with children who weigh more at initiation of HAART.[16-19] This may contribute to a threshold effect and also served as the justification behind the subgroup analysis that was done in this study. We aimed to assess whether the infants/children who were already at a low weight (WAZ < -1) showed different growth patterns. Our results indicated that the growth pattern of the subgroup (n = 51) was similar to the growth pattern of the entire group (n = 98); the largest number of infants/children showed an increase in weight gain. This could be because over half (53.1%) of the infants/children in this study were underweight at baseline (WAZ < -2).

Improvements in Hb levels as well as in CD4 % in this study were significant over the 24 months from initiation of HAART, showing the positive effect of HAART on immunity. There were statistically significant improvements in weight gain over the 24-month research period and at each six-month follow-up visit since HAART was initiated. Weight gain improved significantly from as early as six months, whereas linear growth only started improving significantly after six months. Similar findings have been indicated in the majority of studies in sub-Saharan Africa, where consistent improvements in both WAZ and H/LAZ are common after HAART is initiated, with more rapid increases in weight gain in the first six months compared with more gradual increases in length/height.[16,20] These results indicate that weight improvements take place earlier than height improvements, but that both anthropometrical indicators increase rapidly with HAART duration. Findings from research conducted by Yotebieng et al.[11] also indicated that weight, but not height, was a good indicator of HAART treatment response during the first six months following initiation.

The children in our study did not reach complete catch-up growth after 24 months, as the mean WAZ-score was still low (WAZ = -1.1). The proposal that catch-up growth is cohort-specific has been made previously and so far, only cohorts of children in the United States have reached complete catch-up growth after two years on HAART, when their growth was assessed using growth charts for healthy children.[21] The present study was conducted in a public hospital in a developing setting of South Africa. The complex interaction of environmental factors, programme factors and the impact of poor resources on frequency of opportunistic infections is linked to a weaker immunity[9,22] and these factors may have had a role to play in this study as well. Complex interactions may affect growth parameters and therefore the time taken to catch

up growth in the developing world, where a high prevalence of malnutrition is also diagnosed, is longer than in developed settings.[22,23]

Secondly, this study aimed to compare the interpretations of weight gain patterns of the same group of infants and children according to two different weight monitoring charts: age- and sex-specific HIV weight gain charts, proposed by Yotebieng et al.[1], and weight pattern interpretations according to current WHO[12,13] WAZ. This study found that the weight gain patterns were different in this group of children when interpreted according to the two reference charts proposed. The WHO growth charts indicated that the largest proportion of the infants/children in this study showed an increase in their rate of weight gain, whereas the HIV charts showed that the largest proportion maintained their rate of weight gain. Only a small number of infants/children had a fluctuating weight pattern according to both charts. Of special interest is the difference between interpretations of weight gain in this group: 69% of the infants/children showed an increased rate of weight gain according to the WHO growth charts[12,13] versus only 16% when interpreting weight gain by using a specialised HIV weight gain chart.[1] These interpretations were comparatively statistically different, as proven by the poor agreement between growth patterns. This poor agreement supports the research conducted by Yotebieng et al.[1] who suggest the use of age- and sex-specific charts for infants/children that are HIV-infected and receiving HAART.

It is documented in the literature that children with HIV have lower WAZ and L/HAZ scores when compared with their HIV-uninfected counterparts.[8] The use of WHO growth charts is valid when they are used to monitor growth parameters of the HIV-uninfected population. On the other hand, it is not appropriate to interpret weight gain in the child that was initiated on HAART by using a chart that was constructed with a HIV-uninfected population as reference. The weight gain of children on HAART has been well documented in the literature and therefore it was possible to create reference curves specifically for these children. The key is to remember that HIV-infected children are not all started on HAART when they are born, or even at the same age. The HIV weight gain charts that were constructed for children younger than ten years of age serve as a correct reference that is sex-specific and specific to HAART initiation age and follow-up age. The interpreter is now provided with a population-specific point of reference in terms of the weight gain that is associated with treatment response. Growth charts are essential clinical tools that are user friendly and cheap assessment and monitoring tools for growth evaluation. Their interpretations may have important implications for child health programmes.[24]

Practical implications

The results of this study can help to create awareness of the value of a clinical tool for HAART response monitoring in addition to weight interpretation, which may aid in the improvement of national programmes without the financial burden. Children will be more likely to be 'flagged' using population specific weight gain charts compared to ones that are not population specific.

The correct interpretation of weight gain could assist health workers in identifying treatment failure at an earlier stage; insufficient and excessive weight gain may serve as an early warning sign for the nurse at the clinic to refer the child for medical care or nutritional education.

In addition to the Road-to-Health Booklet (RtHB) in South Africa, the simple tool created by Yotebieng et al.[4] can help the nurse, doctor, specialist, researcher and parent/s or caretakers to interpret the weight gain of the HIV-infected child in terms of response to treatment. This tool should be provided to professionals, while a simplified version may be provided to parents/caretakers. The WHO support the use of clinical parameters such as growth monitoring in environments where viral loads cannot be obtained, especially growth parameters to monitor HAART response.[25] It might also be necessary to create monthly or three-monthly weight gain references, so that weight can be monitored more often and not just six monthly on average, especially when children are young. Again, if health professionals at clinics or even caretakers could monitor weight gain in these children by using a simple reference tool, the child's outcome could be improved by early interventions, whether these be medical interventions, social interventions, feeding programmes, special counselling or improvement of interdisciplinary treatment in any setting.

Limitations of the study

The retrospective design of this study relied on measurements and recordkeeping that could not be controlled and which are susceptible to technical and human error. The researchers did not assess the impact of different ARV drugs on the rate of weight gain, because the study population was too small to study subgroups based on different ARVs. A subgroup analysis of children who were changed from one regime to another would also have been useful.

Recommendations

In terms of recommendations for practice, it is suggested that in children on HAART, weight gain should preferably be assessed against the reference norms that are associated with response to treatment. An interpretation note should be written by a healthcare professional, indicating

whether an infant/child receiving HAART is gaining sufficient weight compared with reference children on HAART.

The new reference charts are more likely to indicate a need for intervention, including nutrition interventions related to either inadequate or excessive weight gain in children on HAART.

In terms of recommendations for further research, more research should be undertaken to determine the impact of nutrition interventions, especially at the early stages of improper weight gain, in order to assess the effect on treatment success and immunity. A positive effect on HAART success and immunity will improve the quality of life of the HIV-infected child and should save money, with potentially fewer children being treated for opportunistic infections. The WHO suggests that more patients have recently been experiencing treatment failure and viral resistance, which increases the need for more expensive second-line regimes.[26]

Conclusion

For this study we recorded and described the growth of a group of infants and children who were initiated on HAART before the age of 10 years old. The most rapid growth improvements were observed in weight. Height also improved significantly, although less rapidly. The children however, did not reach complete catch-up growth after the 24-month study period and the average time of initiation of HAART was later than recommended by the WHO guidelines. In addition, this study compared the interpretations of the weight gain of the infants/children according to usual WHO growth charts versus age- and sex-specific HIV weight gain charts proposed in previous research. The weight gain patterns of the children were different when interpreted according to the two growth charts. The use of HIV weight gain charts is a simple, low cost clinical tool that can aid in the monitoring of HAART response in children.

Future research should aim to investigate the use of disease-specific monitoring tools, such as growth charts. This investigation should not be limited to the HIV setting.

Acknowledgements

The researchers would like to acknowledge all the friendly and helpful nursing staff at the paediatric out-patient clinic of Dr George Mukhari Academic Hospital, especially Sister Katy Thembi Mafotsa, who has a deep love for the children that she treats at the ARV clinic.

Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this article.

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CHAPTER 5: SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

5.1 AIMS OF THE STUDY

The study aimed to investigate the weight gain and weight change patterns of infants/children younger than ten years of age, initiated on highly active antiretroviral therapy (HAART) and monitored primarily in terms of weight changes over a period of 24 months, in order to gain a better understanding of the impact of HAART on weight during human immunodeficiency virus (HIV) infection. In addition, this study also compared the interpretation of weight gain in the same group of children, but according to two different references: the World Health Organisation's (WHO) weight-for-age z-scores (WAZ) (WHO, 2006; WHO, 2007) and the response to treatment indicated by sex- and age-specific norms (Yotebieng *et al*., 2015) that have been constructed from data of HIV-infected infants/children on HAART. A significant difference in interpretation of weight gain could have a major impact on the treatment of a child that is at higher risk of morbidity and mortality, as well as on the timing of the intervention.

5.2 SUMMARY

In this retrospective, quantitative study with its descriptive-comparative design, weight and other data relating to HIV were captured from patient records that were kept from the time that an infant/child was initiated on HAART. A total of n = 98 children, younger than ten years old was included, of which a total of N = 363 weight data points was obtained over a maximum period of 24 months per child. Length/height, biochemical markers and information regarding the progression of HIV infection were also recorded for each child.

The majority of children in our study were already at an advanced clinical stage of HIV infection; according to the WHO clinical classification (WHO, 2007), 69% were classified as clinical stage 3 and stage 4, with only 7% classified as clinical stage 1 and 2. No classification stage was recorded in 24% of the children. The mean age at which HAART was initiated in this group of children was 35.5 months or almost three years old. The mean T-lymphocyte-bearing CD4 receptor (CD4+) cell percentage (%) was 15%, which is classified as severe HIV-associated immunodeficiency, according to the WHO immunological classification for established HIV infection (WHO, 2007) for the age mentioned. More than half of the children (53.1%) were underweight for their age (mean WAZ = -2.1) and more than half (56.5%) were stunted (mean L/HAZ = -2.3) when HAART was started.

Compared with baseline, weight increased significantly from HAART initiation to 24 months and also at each of the 6-month intervals ($p < 0.0001$; AIC = 1 484.9). L/HAZ did not increase

significantly from HAART initiation to 6 months' follow-up (p = 0.058), but increased significantly from baseline to 12, 18 and 24 months (p ≤ 0.001; AIC = 895.3). The mean WAZ curve starts from a z-score of < -2.1, which is in the underweight range for age. The biggest mean improvements were at the 12- and 18-month follow-up periods, with a change from WAZ = -2.1 to WAZ = -1. Compared with baseline, WAZ increased significantly from HAART initiation to 24 months and also at each follow-up (p < 0.0001; AIC = 970.3). Both Hb and CD4 % increased significantly from HAART initiation to 24 months and also between each follow-up visit, compared with baseline (p<0.0001; AIC = 723.1 and AIC = 1 655.3, respectively).

HIV-infected children show a tendency to grow below the healthy standards set for age and sex (Merchant & Lala, 2012). By providing HAART, which induces viral suppression and reduced viral burden (Jaspan *et al.,* 2005), one can expect a shunt in energy usage from an activated and chronic immunological state to a state of positive nitrogen balance with an increase in both weight and height (Miller *et al.,* 2001; Majaliwa *et al*., 2009). In this study, weight and height increased significantly, but weight improved by as early as six months whereas length/height started improving only after six months on HAART.

In another analysis, we investigated the agreement between categories of weight gain patterns. A total of 86 children's individual growth patterns were interpreted according to HIV weight gain charts established by Yotebieng *et al*. (2015) and then interpreted again according to the WHO growth charts (WHO, 2006; WHO; 2007). Statistically, the agreement was poor and insignificant (Kappa value = 0.003, p = 0.95), which indicates that the two mentioned charts actually provided different interpretations of the same group of children. According to the HIV weight gain charts (Yotebieng *et al.,* 2015), most (62.8%) of the infants/children maintained their weight gain for their sex and follow-up time, whilst the WHO charts (WHO, 2006; WHO, 2007) indicate that the largest proportion of the infants/children (68.8%) showed an increase in weight gain patterns. The HIV charts indicated that 16.3% of the infants/children had a decreasing weight gain pattern across percentiles, but the WHO chart indicated that the number of infants/children with a decrease was almost half of that (10.5%). A subgroup analysis was also performed to further investigate the agreement between the two charts, because children with lower weight-for-age tend to have more robust weight increases, but the agreement was still poor and statistically insignificant (Kappa value = 0.03; p = 0.58).

5.3 CONCLUSIONS

The "late" initiation of HAART is a definite concern and should be investigated, especially because of younger children's immature immune systems that increase their risk of death, particularly in the first year of life. This observation may still reflect earlier practices of

introduction of HAART in infants and children only once all clinical and social criteria for treatment have been fulfilled (Department of Health, 2016b). Research suggests that earlier HAART initiation is crucial in order to lower the risk of virologic failure, which is why the goal posts are shifting towards even earlier diagnosis and treatment, ultimately targeting the newborn as well as the perinatally affected patient (Frigati *et al.,* 2014).

Even though the children in this study were severely immunocompromised, they showed rapid weight and height improvements on HAART. Similarly, the literature indicates that children with pre-baseline comorbidities, prior hospitalisations, diarrhoeal episodes or confirmed infectious pathogens managed to catch up anthropometrically when on HAART (Chhagan *et al*., 2012). In this study, however, the children did not manage to reach complete catch-up growth within the 24-month research period, which shows that the unique environment and socio-economic setting of the cohort does affect the rate of growth of infants and children.

Finally, the different weight gain interpretations of the same group of children according to the HIV weight gain charts that are a measure of response to treatment, versus the WHO charts that indicate ideal growth in healthy children, prove that children should be compared with the correct references, especially if they are available, otherwise the clinician, nurse, doctor, dietitian, researcher and caretaker can make a neither a timeous nor a valid intervention decision. A positive effect on HAART success will save money, with potentially fewer children being treated for opportunistic infections. The WHO suggests that more patients have recently been experiencing treatment failure and viral resistance, which increases the need for more expensive second-line regimens (WHO, 2012).

Timing is important, especially when it comes to the care and monitoring of young infants/children. In a setting where blood cannot be drawn or analysed owing to financial constraints or lack of resources, something as simple as the correct weight gain interpretations might save a child's life.

5.4 RECOMMENDATIONS

More nutritional research is needed to determine the impact of nutrition interventions, especially at the early stages of improper weight gain, in order to assess the impact on HAART treatment success and immunity.

The proposal that growth monitoring may be a surrogate marker for viral suppression (VS) has been made previously (Benjamin *et al.,* 2003), but more research is needed to improve the description. Length/height gain references have to date not been established and future

research should investigate its association with HIV progression. A previous study by Benjamin *et al*. (2003) suggested that height velocity should be considered as a composite clinical endpoint in future trials in paediatric HIV. In many instances, height is not routinely recorded.

Although the meaningful recording of anthropometrical measurements is absolutely essential, it is lacking. Growth *curves* (meaning more than one plotted measurement) provide valuable information regarding the individual infant/child's growth, by telling a progress "story". Raw weight and/or once-off plotted weight recordings are almost impossible to interpret with value. A simple interpretation of the amount of weight gain could improve inter-professional communication and thus the care of an HIV-infected child.

In addition to the Road-to-Health Booklet (RtHB) in South Africa (NDOH, 2016a), the simple tool created by Yotebieng *et al.* (2015) can help the nurse, doctor, specialist, researcher and parent/s or caretakers to interpret the weight gain of the HIV-infected child and should be provided to professionals. A simplified version may be provided to parents/caretakers, together with education, so that they can also monitor their children at home. It might be necessary also to create monthly or three-monthly weight gain references, so that weight can be monitored more often and not just six monthly on average, especially in infants and young children. Again, if clinics or even caretakers could monitor weight gain in these children by using a simple reference tool, the child's outcome could be improved by early interventions, whether these be social interventions, feeding programmes, special counselling or the improvement of interdisciplinary treatment in any setting.

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ADDENDUM A: HREC CERTIFICATE

ADDENDUM B: SMUREC CERTIFICATE

ADDENDUM C: HOSPITAL PERMISSION LETTER

ADDENDUM D: ARV CLINIC PERMISSION LETTER

ADDENDUM E: PUBLISHING GUIDELINES