Treatment outcome of HIV-1 infected children on antiretroviral therapy in the Limpopo Province of South Africa

By

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DEDICATION

This work is dedicated to my daughters, Anu and Nkolaka and my son, Ngu

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DECLARATION

This study was carried out under the supervision of Prof. Debra Jackson of the University of the Western Cape and co-supervised by Prof Pascal O. Bessong of the University of Venda.

I hereby declare that the study represent the original work of the author and has not been submitted in any form to the above Universities or any other University. Where use has been made of the work of others, it has been appropriately acknowledged in the text.

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Asongna Theresia Forkem Folefoc Date

LIST OF ABBREVIATION

µL	microlitre
3TC	Lamivudine
AIDS	Aquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
CD4	Cluster of Differentiation 4
CI	Confidence Interval
d4T	Stavudine
DoH	Department of Health
HAART	Highly Active Antiretroviral Therapy
HAPG	HIV/AIDS Prevention Group
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
Kg	Kilogram
LPV/r	Lopinavir/Ritonavir
LTFU	Loss to Follow-up
mm^3	cubic millimeter
MTCT	Mother-to Child Transmission
NVP	Nevirapine
PHC	Primary Health care
PMTCT	Prevention of Mother-to-Child Transmission
STD	Sexually Transmitted Disease
UN	United Nations

UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
VCT	Voluntary Counseling and Testing
WAZ	Weight-for-age
WHO	World Health Organization

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ABSTRACT

Background

HIV is a worldwide pandemic with an estimated 2.5 million children under the age of 15 living with HIV in the world in 2009. Children account for approximately 14% of all HIV-related deaths around the world. Several studies have shown that the use of antiretroviral drugs greatly improve the lives of HIV-1 infected individuals, however, most of these studies report on outcomes of ART programmes in developed world and for adult patients. Very few settings have published outcomes of paediatric ART programmes.

Objectives

This research was aimed at describing the long term (at least one year) treatment outcome of HIV-1 infected children in the HIV/AIDS Prevention Group (HAPG) program in Bela-Bela in the Limpopo province of South Africa.

Study design and methods

A quantitative approach involving a retrospective cohort design was used for the study. The study included all children under the age of 15 that were enrolled in the HATG treatment programme in Bela-Bela between February 2004 and December 2009. Immunological, virological, clinical outcomes and loss to follow-up were determined for this cohort. Mortality and survival was also determined.

Results

The median age of children in this study was 5 years (IQR: 2-7) with 14% (10/71) of them being less than 18 months. Median CD4 count at commencement of ART, viral load and weight were 358

cells/mm3 (IQR 203.5-, 125673 RNA copies/µL (IQR 58094-328424.5) and 14.5Kg (IQR: 11.0-18.35) respectively. CD4 counts and weight showed increase within the study period, and there was also a decline in viral load. Loss to follow-up was 7.04% while mortality was 19% with 21.43% of mortality cases being children who were ≤18months. Mortality occurred within the first year of ART initiation and occurred in cases that had advanced disease.

Conclusion

This study shows that the ART program in Bela-Bela has a positive outcome on HIV positive children. The high mortality rate was due to children starting ART at an advanced disease stage. Despite the good outcome, it is recommended that a system be put into place that will aid in identifying children at an early stage of the disease and treatment initiated promptly.

CHAPTER 1: INTRODUCTION

1.1 Introduction

It was estimated that 2.5 million children who are under the age of 15 years were living with the human immunodeficiency virus (HIV) around the world in 2009 (UNICEF, 2010). Approximately 430,000 new infections were reported in this same year and about ninety percent of the estimated number of children living with HIV is found in Sub-Sahara Africa (Barth *et al*, 2010). New infections in children are believed to be due to mother to child transmission (MTCT) either *in utero*, during delivery or through breastfeeding. In total, children account for 8% of all HIV infections and 14% of all HIV-related deaths (UNICEF, 2010).

Several challenges are faced by resource-limited countries in the delivery of antiretroviral treatment (ART) to children under the age of 15 years. These challenges range from lack of early diagnosis and monitoring techniques, lack of health care infrastructure, limited availability of paediatric ARV formulations, lack of human resources in pediatric HIV care delivery, and limited funds to sustain treatment programmes (Paintsil, 2007). Despite these challenges, some countries with limited resources for pediatric ART delivery still report good treatment outcomes that are comparable to those in high-income countries (Sutcliffe et al, 2008).

South Africa has the largest paediatric antiretroviral treatment (ART) programme in the world, with an estimated 32 000 children under 15 years of age receiving treatment at the end of 2007 (WHO, UNICEF, UNAIDS, 2008). 1n South Africa, the proportion of newly infected children starting ART increased from 2.1% between mid-2002 and mid-2003, to 36.9% between mid-2007 and mid-2008 (Department of Health [DoH], 2009). Variation in access to ART for children exists between provinces with the Western Cape having coverage of 96.9% in the 2007/2008 period while only 22.1%

of children in the Free State were able to access ART (DoH, 2009). Variations can also be seen within provinces with children in urban areas having more access than those in rural areas.

Generally, contextual factors may play a role in the success of interventions. These factors may include political will and leadership, the status of women, stigmatization of high risk groups and the presence of armed conflicts and social unrest (Campbell, 2010). In the case of children, outcome of treatment may be linked to adherence which is influenced by factors such as dosing, medicine formulation (children being reluctant to take the drugs in powder or syrup form due to their unpleasant taste), dietary restrictions and toxic side effects. The socio-economic status of children may also influence adherence (Fennel, 2010). In rural Limpopo, social factors that influence treatment outcome include stigma, the practice of faith healing and certain traditional practices (Campbell, 2010). Even though access to most HIV treatment programmes are free, the quality of care and the distance to treatment centres contribute to the utilization of these programmes and therefore the outcome.

1.2 Problem statement

Intervention measures to fight against HIV/AIDS include measures that target behaviours, social and cultural drivers of the disease and also biological drivers. Though prevention efforts to reduce the transmission and spread of the disease will help curb the pandemic, there is the need to treat those who are already infected which doubles as a preventive and a control measure. Treatment programs around the world have shown positive effects on patients but these programs have not been replicated in some resource limited settings. It is essential that policy makers and program planners have full description of intervention measures and estimates of the effect of interventions on a group of people or the public to be able to make appropriate decisions that will affect research and funding for particular programs.

In South Africa, treatment with ARVs is of great importance due to the high burden of disease in the country. Many treatment programs have been evaluated and recommendations made to policy makers, however, most of these programs are focused on adult and in better resourced clinics particularly in urban areas (Davies *et al*, 2009; Ingle *et al*, 2010). In some rural programs, virologic data are usually not available and in certain cases, virologic, immunologic and clinical data where available, are limited to short term follow-up (approximately 1 year follow-up) with very few studies reporting on outcome after 3 years of follow-up (Barth et al, 2011). Since the start of the HIV treatment program by the HIV/AIDS Prevention Group (HAPG) in Bela-Bela in the Limpopo province, there has been no published study that describes the outcome (short- or long-term) of this program.

Consultation for this project started mid January 2011, initially between Dr. Bessong Pascal (Head of Microbiology Department and Head of the AIDS research Laboratory at the University of Venda) who is one of the board members of the HAPG and Ms Cecile Manhaeve who is chair of the board and also actively participate in the day-to-day running of the clinic in Bela-Bela. Their discussion centered on the lack of information on the outcome of the program since its initiation. By the end of February 2011, in consultation with a statistician, it was agreed that this study be conducted. Formal discussions with Dr. Bessong, Cecile, Prof Amey (the statistician) and myself concerning the children (<15 years) aspect of the study has taken place and there is constant communication amongst us on the different aspects of the study (including the adult outcome and the overall outcome of the program).

CHAPTER 2: LITERATURE REVIEW

2.1 The HIV/AIDS pandemic

The Human Immunodeficiency Virus type 1 (HIV-1) has been identified as the etiologic agent causing the acquired immunodeficiency syndrome (AIDS). AIDS is a condition in humans that cause the immune system to fail leading to a decrease in the ability of the system to fight disease therefore allowing opportunistic infections and certain cancers to thrive. The HI virus can be transmitted in many different ways. The majority of infections are acquired through unprotected sexual intercourse (vaginal or anal) with an infected individual. Sharing of contaminated injection materials and sharps constitute an important transmission route. Transfusion of contaminated blood and blood products has also been documented. Transmission from mother to child *in utero*, during delivery or through breastfeeding is the predominant method of infection in children (WHO 2012 fact sheet).

Since its discovery approximately three decades ago, AIDS has been identified as the most deadly infectious disease in the world with WHO and the UNAIDS estimating over 25 million deaths due to HIV/AIDS (UNAIDS, 2010). In 2010 alone, approximately 2.8 million people died of HIV/AIDS. An estimated 34 million people were living with HIV/AIDS world wide by the end of 2010, with an estimated 22.5 million from Sub-Sahara Africa which remains the region most affected by the pandemic. Sub-Sahara Africa alone accounts for approximately 67% of infections worldwide and experienced a 1.2 million deaths from the disease in 2010 alone (UNAIDS, 2010).

The epidemic in South Africa remains one of the highest in the world with an estimated 5.6 million people living with HIV at the end of 2009 and over 48,000 new infections in 2010. Deaths due to AIDS in South Africa in 2009 was estimated at 310,000. A variation exists in the prevalence of HIV in

South Africa based on age, gender, race, socio-economic status and geographic location. HIV prevalence ranges from as low as 18.4% in the Northern Cape Province to as high as 39.5% in KwaZulu-Natal province. The prevalence in Limpopo in 2010 among antenatal clinic attendees was 21.9% increasing from14.5% in 2001 and 20.7% in 2007 (UNAIDS, 2010; DOH, 2011). Prevalence in the overall Limpopo population for 2008 was estimated at 8.8%.

2.1 HIV Prevention and Treatment

With an almost thorough knowledge of how the virus is transmitted, and advances in the knowledge of its life cycle, molecular structure and its interaction with its host, many different methods have been designed to fight HIV and AIDS. Prevention in the context of HIV/AIDS involves preventing transmission and spread of the virus, preventing and controlling infection by opportunistic microorganisms and slowing the transition from virus infection to AIDS development. One of the most celebrated measures that have been used to fight major infectious diseases in the past has been the use of vaccines. Development of a safe and efficacious vaccine against HIV remains one of the top global health priorities and the best solution for the long term prevention and control of HIV/AIDS. There have been several attempts at vaccine development and trials (Rerks-Ngarm *et al*, 2009; Buchbinder *et al*, 2008) but to date, there is no approved vaccine against HIV/ AIDS. While research in the field of vaccine development continues, other measures have been and are still being put into place for the prevention and control of the pandemic.

Measures that target risk behaviours such as the number of sex partners, unprotected sex and the sharing of contaminated needles have been shown to reduce HIV transmission (Cohen *et al*, 2004; Johnson *et al*, 2008). Voluntary counseling and testing (VCT) has also been shown to reduce some of these risk behaviours. Strategies that incorporate societal and cultural drivers of the disease such as stigmatization, discrimination, poverty, inequality, lack of education, migration and homelessness, can

also help prevent transmission and spread of HIV. Prevention and treatment of sexually transmitted diseases (STDs) constitute an important part of the fight against HIV. Studies have shown association between certain STDs and HIV (Mmbaga *et al*, 2011; Atashili *et al*, 2008). A study in South Africa that used a mathematical model to simulate the interaction between HIV and six STDs and two common vaginal infections (bacterial vaginosis and vagina candidiasis) revealed that these infections have significantly contributed to the spread of HIV in South Africa. The authors acknowledge that although the control of STDs has not shown great impact on South African HIV incidence because of late introduction and suboptimal coverage, control of STDs may go a long way to control HIV/AIDS (Johnson *et al*, 2012). The use of topical microbicides can also help prevent the spread of the disease (Klasse *et al*, 2006).

2.3 Prevention of mother-to-child transmission (PMTCT)

PMTCT can help reduce the number of children infected with HIV. Without any intervention, WHO estimates that the rate of transmission from mother to child could range from 15-45%.

Over the years, guidelines for the PMTCT have been updated however, all recommendations are based on evidence and are aimed at improving the health of both mother and child and reduction of transmission. WHO recommends that all HIV positive pregnant women who meet the criteria for treatment based on either clinical staging or CD4 counts should receive treatment. In this respect, women with CD4 counts less than 350/mm^3 should receive treatment irrespective of the stage and women at stage 4 of the disease should receive treatment irrespective of CD4 counts (WHO, 2010 fact sheet; WHO, 2007)). WHO recommends a twice daily dose of AZT for the mother and her infant as prophylaxis and either AZT or Nevirapine (NVP) for a period of six weeks after birth for a non-breastfeeding infant. For breastfeeding infants, a daily prophylactic treatment with NVP for up to one week after the mother stops breastfeeding. A second option involves a three-drug prohylaxis during

pregnancy and throughout the breastfeeding period including prophylaxis for the infant for six weeks after birth, irrespective of whether the infant is breastfeeding or not (WHO, 2010 fact sheet).

In 2008, The South African Department of Health decided to institute a dual antiretroviral treatment as standard care for pregnant women whose CD4 counts were >200/mm^3 and those with CD4 counts <200/mm^3 were considered eligible for triple therapy. This guideline was changed in 2010 to provide triple antiretroviral treatment for all pregnant women with CD4 counts <350/mm^3 (DOH, 2010).

Treatment with antiretrovirals (ARVs) has been considered one of the most successful measures for HIV/AIDS prevention. Since the introduction of ART and the use of highly active antiretroviral therapy (HAART), there has been great improvement in the lives of people living with the disease with dramatic decrease in morbidity and mortality over the years. The UNAIDS reported a 17% increase in the number of people living with HIV/AIDS from 2001 to the end of 2010. In a negative light, this increase portrays an increase in prevalence, but in a positive light, it reflects the success of the use of ARVs in prolonging the lives of people infected with the virus. It was estimated that deaths due to AIDS decreased to 1.8million at the end of 2010 compared to 2.2 million in the mid 2000s (UNAIDS 2011) due to increase in access to antiretroviral drugs. Approximately 15 million people worldwide have access to ART. The benefits of ART have been echoed in many settings around the world (Dlodlo *et al*, 2011; Reniers *et al*, 2009; Jahn *et al*, 2008). ARVs are known to reduce viral replication, thereby reducing viral load. Since viral load is a strong predictor of virus transmission between discordant partners, it is but evident that reduction in viral load through the use of ARVs will greatly reduce transmission of the virus between partners and therefore prevent the spread of the disease (Cohen *et al* 2011; DeGruttola *et al*, 2010). Although treatment brings forth hope in the fight against HIV/AIDS, ART to date is still expensive in some low and middle income settings and

adherence poses a problem due to the high pill burden. It is therefore important that treatment be used in conjunction with other prevention strategies to be able to achieve maximum results.

2.4 HIV/AIDS in children

WHO, UNAIDS and UNICEF in their 2011 report estimated that more than 3.4 million children under the age of 15 were living with HIV/AIDS at the end of 2010. An estimated 3.1 million of these children were from Sub-Saharan Africa accounting for 90% of the global infection in children. Approximately 390,000 new infections were registered for children in 2010. Like in adults, HIV in children can be transmitted through transfusion of infected blood or blood products, or use of unsterilized needles. Sharing of contaminated needles and syringes among homeless and street children for injecting drugs may also lead to transmission of the virus. Another mode of transmission may be through sexual intercourse. Although not a major mode of transmission in children, it may occur in communities where children become sexually active at a young age or when they are sexually abused or raped.

Unlike in adults, the majority of children acquire HIV through mother-to-child transmission (MTCT) either during pregnancy, during labour and delivery or through breastfeeding (UNAIDS). It is estimated that without treatment, approximately 15-30% of children who are born to HIV positive mothers will be infected with the virus either *in utero* or during delivery while a further 2-20% will acquire the virus through breastfeeding (WHO 2006b).

2.5 HIV prevention for children

Since most cases of HIV in children occur through mother-to-child transmission, prevention of MTCT remains a major step towards reduction of the number of children infected with HIV/AIDS. PMTCT can be achieved through treatment with ARVs during pregnancy, childbirth and breastfeeding. Studies in resource-rich countries have shown that administration of Zidovudine during pregnancy and peripartum period lead to an initial reduction of perinatal transmission of HIV by 67% and a subsequent reduction in perinatal transmission by 98%-99% with the use of highly active antiretroviral therapy (HAART) during pregnancy (Paintsil, 2010). A study in Africa has also shown that mothers who took triple combination antiretroviral drugs during pregnancy had a reduced risk of transmitting the virus to their babies than women who took Zidovudine and single dose nevirapine (The Kesho Bora Study Group, 2011). To date, UNAIDS estimate that more than 350,000 new cases of HIV in children has been prevented through prophylactic treatment of HIV positive pregnant women (UNAIDS, 2011). These results, though very impressive, have not been achieved in most resource-limited countries. UNAIDS estimated that only about half the number of pregnant women requiring drugs to prevent transmission to their babies were able to access them. Greater awareness and improvement in the availability of counseling, testing and treatment services still need to be provided in many resource-limited settings.

A comprehensive approach to PMTCT was instituted by the UN which involves a four prong strategy. These strategies are:

The primary prevention of HIV infection among women, especially those of childbearing age. For this approach, it is expected that prevention of infection in would-be parents and lactating mothers will eventually prevent infection of their children. Improvement in reproductive health services such as antenatal, postpartum and postnatal care including community support may help achieve this strategy.

The second prong is to prevent unintended pregnancies in HIV infected women which will help reduce the number of babies born with the disease. In this case, VCT and family planning services need to include a system for support of such women and counseling that can help them make informed decisions concerning childbearing. The third prong is targeted at women who are already HIV positive and are either pregnant or breastfeeding. This approach is aimed at preventing the disease being passed on to the unborn child or the breastfeeding infant. This can be achieved through access to antiretroviral treatment both for the infected mother and the infant. A fourth strategy involves the provision of treatment, care and support for HIV positive women, their infants and their family as a whole. This strategy aim at better integration of treatment, care, family and community support.

The success of the UN strategies in reducing MTCT varies from country to country due to commitment and even within the same country due to coverage and access to ARVs, however, there have been reports of comprehensive programs that helped reduce MTCT in many resource limited settings (WHO 2010c).

2.6 HIV/AIDS treatment in children

While prevention of MTCT may help reduce the number of children with HIV/AIDS, treatment with antiretrovirals is currently the best option for children who are already infected (WHO, 2006a). It is estimated that without ART, about one third of children may not live to see their first birthday while more than half of them die before their second birthday (Barth *et al*, 2011; UNICEF, 2010; Becquet *et al*, 2012). In a cohort study that aimed at determining the survival of new born based on the infection status of their mother, the infants and the time at which infection occurred, Chopra and collaborators studied 883 mothers and their infants. Their cohort composed of 665 HIV positive and 218 HIV negative mothers. They found that 28.4% of children who were exposed to HIV died before six weeks

while 56.7% died by the twelfth week. These authors also reported that 81.3% of infected infants who died were infected by their third week of life stressing the need for strategies to prevent early infection and provision of antiretrovirals to eligible infants (Chopra *et al*, 2010). Treatment with antiretroviral drugs helps slow progression of the disease and has been shown to greatly improve the health of HIV/AIDS patients by decreasing morbidity and mortality due to AIDS. In South Africa, a collaborative cohort that represented 20% of children in the South African national treatment programme was used to assess paediatric ART outcome and their associations (Davies *et al.*, 2009). This cohort involved 7 public sector paediatric programmes in three provinces (Gauteng, Western Cape and Kwazulu Natal) and included 6,078 ART-naïve children who were ≤16 years old and who started treatment with ≥3 ARV before March 2008. The study which used time to death or loss to follow-up, immune status and virological suppression as outcome measures was able to demonstrate dramatic clinical benefits for children accessing the national ART programme. These authors reported that 82.4% of children experienced virological suppression at 3 years of follow-up while only 16.9% and 6.4% were severely immunosupressed at 1 and 3 years respectively. Mortality rate for the cohort was 7.7% and an impressive 81.1% of the children were alive and still in care at 3 years. There was however, a high mortality rate among infants and children with advanced disease, thereby stressing the need for early diagnosis and treatment. Despite the positive impact of ART on children in this study, the authors acknowledged some limitations which included the non-inclusion of high burden provinces, the disproportionate representation of sites with tertiary care facilities and the changing of the WHO staging system which limits its value as a measure of disease progression (Davis *et al*, 2009)

In Zambia, an open cohort assessment that used routinely collected data on clinical and immunological responses from the medical record system in 18 government primary health facilities in Lusaka showed good clinical and immunological outcome of children on ART (Bolton-Moore et al, 2007).

The study was aimed at determining secular trends in the characteristic and treatment outcomes of children on ART in both rural and urban clinics in Zambia and outcome results were reported for each year. In this study, since the authors relied on data abstracted from patient medical records, there is the likelihood that some relevant information may not be present and available data may not be complete. This fact is acknowledged by the authors for data on anthropometric and laboratory measures (Bolton-Moore *et al*, 2007). In addition, it is possible that as the years go by, there are improvements in the running of such programmes and methods of data collection which may be reflected in results obtained for later years of the programme. Despite these concerns about the study, it is evident that ART initiation at an early stage for children can greatly improve outcome of the disease. Analysis of data from 1561 children receiving ART who fitted their inclusion criteria, showed that the median CD4 cell percentage increased from 12.9% at ART initiation to 27.0% and 28.4% after one and two years of ART respectively.

A retrospective cohort study that involved HIV positive children that were followed up for four years in two HIV-programmes in Cambodia also showed impressive outcomes but with high mortality and loss to follow-up rates before and during the early periods of ART (Raguenaud *et al*, 2009). This study had a sample size of 1168 HIV positive children and sought to measure mortality in both pre-ART children and children already on ART. A high mortality and loss to follow-up rate (14.5% and 5.5% respectively) was experienced in pre-ART children compared to those on ART (22% and 2% respectively). The authors suggest that improvement in such programme outcome may be achieved by more timely initiation of ART (Raguenaud *et al*, 2009). Although this study draws strength from its large sample size and the fact that data came from a programme setting, it also had some limitations. The causes of death were not reliably ascertained, however, the authors note that since both programmes were situated close to a provincial hospital and that doctors performed all consultations,

the level of errors in this respect was limited. Another limitation to this study was the loss to follow-up rate in the pre-ART patient group which may have led to unreported deaths and consequently an underestimation of the mortality rate ratio between the two study groups (Raguenaud *et al*, 2009).

Another study that looked at 4-year outcome from the pediatric outpatient service at the Chris Hani Baragwanath Hospital showed that majority of children in the study achieved viral suppression but also high mortality rate (14.5% [95% CI 11.59-18.51]during the first three months and 3.2% [95% CI: 1.8—3.0] after three months of ART (Meyers *et al*, 2011). The children also experience a doubling of mean CD4 percentage within 12 months of ART initiation increasing from 12.7% to 25.1% with a slower rise to 27.9% and 30.6% at 24 and 36months respectively. The high mortality rate during the early periods of treatment in most ART programmes may reflect the fact that children are not diagnosed early during infection and points to the need for increased awareness of MTCT and better and improved methods to detect infection early and start treatment promptly.

Several other studies in Africa and other resource-limited countries have shown clinical, immunological and virological outcomes of children on ART similar to those in high income countries (Sutcliffe et al, 2008). However, these data are mostly available from urban settings with very few studies being dedicated to the analysis of data from ART programmes in rural areas. A study on the clinical outcome of HIV-infected children on ART in a decentralized nurse/counselor-led programme in KwaZulu-Natal showed that good clinical outcomes can be achieved in rural settings (Janssen et al, 2009). Using a sample of 477 HIV positive children and survival, mortality and changes in laboratory parameters (CD4% and viral load) as outcome measures, the authors were able to show improvements in patients on ART. They showed that the median CD4% increased from 17% to 22% within 6-12 months after initiating ART while 73.5% of those whose viral load data were available had a

suppression in viral load (<25copies/ml). Mortality was 6.7% while 3.7% were lost to follow-up Similar outcome was observed in a retrospective (2-4 years follow-up) cohort of 735 HIV positive children in Ndlovu Medical Centre, in rural Limpopo with 63% of children experiencing viral suppression within a median of 3 years after initiating ART (Barth *et al*, 2011).

Despite these impressive outcomes, access to ART especially for children in resource limited settings still remains a problem. WHO reported that at the end of 2009 only 38% of HIV-infected children who were less than 15 years of age in resource-limited countries needing ART were on therapy (WHO, 2010b). Indicators used to determine coverage of antiretroviral treatment suggest that adults have greater access to ART than children. However, a substantial improvement in access to ART for children has occurred over the past years (Unicef, 2010) with the biggest increase seen in low- and middle- income countries where approximately 456,000 HIV-infected children were on ART by December 2010, an increase from 275,400 in 2008 and 71,500 in 2005 (UNAIDS, 2011; Barth *et al*, 2011).

South Africa, which has the largest pediatric antiretroviral programme in the world, has also seen an increase in access to ART over the years with more than 36% of HIV-infected children accessing treatment by mid 2008 up from 9.4% in mid 2005 and 2.1% between 2002 and 2003. Despite this improvement, ART programmes have not been able to reach more than half of the children needing treatment based on the national guideline (Davies, 2009). Few data are available that demonstrate the success of ART programmes particularly on the virologic outcome of treatment which is very important in predicting drug resistance and long-term sustainability of ART programmes (Moultrie et al, 2009). In most areas where there is lack of proper laboratory information on virological outcome, clinical or immunological decline are usually used to predict treatment failure. However, these

measures and virological failure have shown limited correlation as reported by some studies (Barth *et al*, 2010).

The main goal of antiretroviral treatment is to attain a suppression of viral replication and restore immune function (Paintsil, 2010). Viral load, CD4 counts (or percentage) in addition to clinical outcomes, which are usually manifested by changes in weight and presence or absence of opportunistic infections are the outcome measures that are usually used to assess ART programmes. Monitoring ART in both resource-rich and resource-poor settings is essential in identifying cases of treatment failure which may provide a guide for alternative treatment and also to determine the extent to which ART programmes can be strengthened. Comparing data across different settings can help identify programmes with greater need.

The World Health Organization (WHO, 2010a) has published a technical report which provides guidelines for care of infants and children on ART to help guide health care workers who are involved in pediatric ART delivery in resource-limited settings. This list provides the minimum standards of HIV care and the type of information to be collected at each clinic visit. Collation and analysis of the data collected over a long period of time will be useful in evaluation of local and national programmes and standardization of the process of data collection will aid in identifying the strengths and weaknesses of ART programmes (WHO, 2010a).

2.7 Rational

ART has been shown to provide significant benefits to children accessing them and some rural settings have reported excellent outcomes (Barthe *et al*, 2011; Janssen *et al*, 2009).

This study was aimed at describing the long term (at least one year) virologic, immunologic and other outcomes of HIV positive children in the Bela-Bela treatment programme. This study was part of a

research carried out by the Microbiology and Statistics Departments of the University of Venda that was aimed at determining the overall outcome of the HAPG in Bela-Bela. Information on treatment outcome may help in assessing progress and effectiveness and therefore identify ways to optimize overall performance of the antiretroviral therapy programme. It may also be used to predict long-term programme sustainability.

2.8 Aim of study

The aim of this study was to describe the long term (> 1year) treatment outcomes of HIV-1 infected children in the HIV/AIDS Prevention Group (HAPG) programme in Bela-Bela in the Limpopo province of South Africa.

2.9 Objectives

1. To describe the virological response of HIV-infected children to antiretroviral treatment (ART)
2. To describe the immunological response of HIV-infected children to ART.
3. To describe the clinical outcome of children on ART
4. To describe loss to follow-up of HIV-infected children.

CHAPTER 3: METHODOLOGY

3.1 Study method and design.

A quantitative approach was used for this study employing a retrospective cohort design. In this type of study design, available information on previous exposure is obtained for a defined population and then the outcome determined for this population. This type of study takes a look backward and examines exposures to suspected risk or protection factors in relation to an outcome of interest. The researcher starts the study at the designated time zero and then follows up subjects for the study period which has already taken place (Euser *et al*, 2009).

In this study, the records of a group of children (a cohort) who were HIV positive and who have been exposed to antiretroviral treatment were examined. Routine data on CD4 level, viral load, weight and other measures that were collected at baseline and every three months after initiation of antiretroviral treatment were obtained and analyzed to determine the outcome of the programme on pediatric HIV.

3.2 The setting

Bela-Bela is a peri-urban town in the Limpopo Province situated 100 km north of Pretoria. It has a population of approximately 63,000 people and an unemployment rate of 21% (De Koker et al, 2010; Ndjeka and Manhaeve, 2006). In 1996, community members in Bela-Bela who were concerned about HIV/AIDS formed the HIV/AIDS Prevention Group (HAPG). This group provides voluntary counseling and testing (VCT), and care and support to HIV/AIDS patients. Their activities range from prevention campaigns to free VCT and ART. They also provide home-based care and care for orphaned children, particularly HIV/AIDS orphans. This group was selected as one of the sites in South Africa for the roll-out of ART with funding from the United States President's Emergency Plan

For AIDS Relief (PEPFAR) (Ndjeka and Manhaeve, 2006). Patients who are referred to the HAPG by the local clinic and private doctors are included for treatment based on the following criteria: CD4 count of <200/mm^3 and/or WHO stage IV HIV disease.

3.3 Study population and sample size

All antiretroviral treatment naïve children under the age of 15 that were enrolled in the HATG treatment program in Bela-Bela and started ART between February 2004 and December 2009 were included in this study. The ages of the children were obtained from their birth certificates during admission/registration to the program. In very rare cases where a birth certificate was not available, a road-to-health card was used to ascertain the date of birth. Children who came in from different clinics or from neighbouring countries (e.g Zimbabwe) had to provide proof of HIV testing. In cases where such proof was not available, another HIV test was conducted and the result kept in the file of the patient. ART was initiated in these children following the guidelines of the South African Department of Health.

A total of 71 children were enrolled during this period. A record of all HIV positive children enrolled within this period was obtained from the clinic. Sampling a smaller number may not produce results that reflect the true outcome of the programme (a particular outcome may be due to chance). A higher number of samples could have been better, however, this was not possible since only this number of children were enrolled in the program within the study period.

3.4 Data collection

A quantitative method was employed for data collection since the study involved quantification of relationships between variables. A list of all the children in the program and their files (which included follow-up sheets) were obtained electronically from the clinic. Information from structured patient files, and follow up sheets that were routinely recorded were entered into a specific HIV-database. These data included information on age, sex, weight, CD4 counts and viral load (Appendix 1) obtained on the day of enrolment and subsequently, every three months after treatment has been initiated. For the weight, a medical electrical digital scale was used for weighing the children. CD4 counts and viral load determination were done by TOGA laboratory in Kempton Park, Johannesburg. Blood samples were sent weekly to the lab for CD4 counts and viral load and results sent by Email or extracted from the laboratory's website using specific codes. Information on the type of regimen and other infections associated with AIDS were also extracted from the patient file (Appendix 1).

3.5 Reliability and validity

Validity refers to the degree to which the results of a study are likely to be true and free of bias. Due to the retrospective nature of this study measurement bias could not be overcome since it relied on already existing information. All children in the study period were included in the study reducing selection bias for this population, however generalizability could be affected depending on how the study population compares to other potential target populations. .

Bias and confounding due to data analysis on the other hand can be reduced in order to achieve a high level of validity. Since the nutritional status of the children could not be ascertained and younger children can loose weight more rapidly in the face of disease than older ones, children were grouped according to their age (≤18 months and >18months) and compared for each treatment outcome.

There could be unmeasured confounding that could potentially affect the result of this study. These included; inaccurate reporting of age (date of birth) in cases where a birth certificate or a road to health card is not available to confirm it and also inaccurate recording of information, as well as other socio-demographic factors not generally found in the medical record.

The reliability of a study refers to the reproducibility of the measures of such study if they were to be re-tested. The reliability of this study was ascertained based on the number of samples that were analyzed. The sample size provided for a 95% confidence interval of ±10% for descriptive estimates.

3.6 Data analysis

Outcome measures for this study were virological suppression, CD4 counts, weight and loss to follow-up. Loss to follow-up was defined as a patient who missed two consecutive clinic visits. Those who were lost due to death or moved to the adult group were not considered LTFU.

All information entered into the clinic electronic record at the time of child visit to ARV clinic by clinic staff was obtained from the clinic. This data was then exported on an Excel spreadsheet. The data was cleaned and imported into the statistical programme, SAS for statistical analysis. Basic frequencies were used to determine trends in categorical data while means and medians were used for continuous data. A comparison of CD4 count and viral load by age and gender was assessed. Immunological and virological outcomes were assessed by respectively determining the median CD4+ T-cell and viral load within the study period. Clinical outcomes were assessed by determining the proportion of children who were underweight within the period of study.

Three models were fitted with CD4+, viral load and weight as response variables. A fixed effect linear mixed model was used to analyze the data. The linear mixed model allows a flexible approach to modeling longitudinal data. The linear mixed model handles unbalanced data with unequally spaced time points and subjects observed at different time points. Using all the available data the analysis

directly models the covariance structure and provides valid standard errors and efficient statistical tests. CD4+ cell count and viral load were transformed using natural log to make sure the distribution was close to normal distribution. All analyses were conducted using SAS version 9.3 (SAS Inc., Cary, North Carolina). The variables were defined as significant at 5% level of significance.

Survival time (time from first treatment to death) was evaluated by Kaplan-Meier survival analysis and multivariate Cox proportional hazards modeling. Variables that were significantly associated with death in univariate analysis at the p= 0.2 level were chosen for inclusion for evaluation in multivariate modeling. Only those variables that retained significance ($p<0.05$) in the multivariate model were further included in the final model. Potential independent predictor variables were evaluated for colinearity by examining non-parametric rank correlation coefficients and a variety of models were tested and compared using the -2log likelihood measures for goodness of fit.

For children who were lost to follow-up, data were censored as of the last date of clinic visit and they were not considered to have died.

3.7 Ethical considerations

A letter of permission allowing the Department of Microbiology of the University of Venda to use data from the treatment was obtained from the HAPG board (Appendix 2). The names of the patients whose information were used were kept confidential. Once extracted to Excel, names were deleted and only record numbers were used. Individual data were presented only as aggregate results. No known risk to the patient was associated with this study and no patient benefitted personally from the research. However, results from the study may help in the design of HIV treatment programmes in future. The findings of this research will be shared with the HAPG board. The study was approved by the UWC Higher Degrees and Research Ethics committees.

CHAPTER 4: RESULTS

4.1 Characteristics of Subjects at ART initiation

A total of 71 children were included in this study. The median age for the study participants was 5 years (interquartile range, 2-7) with 8.8% (6/71) of them being 18 months or less. Thirty five children (49.3%) were females. The median CD4+ T cell count at ART initiation was 358 cells/mm^3 (IQR 203.25-570.75cells/mm^3) while the median viral load was 125673 (IQR 58094-328424.5 viruses/µL). The median weight at ART initiation was 14.5kg (IQR 11.0-18.35) (Table 1).

4.2 ARV Treatment

In all cases, children started triple combination drugs of stavudine (d4T), lamivudine (3TC) with either effavirenz (71.8%). lopinavir/ritonavir (14.1%) or Nevirapine (5.6%). Two (2.8%) patients started with Lamivudine-zidovudine-effavirenz combination while a single patient had zidovudine-lamivudine-nevirapine combination regimen. At ART initiation, 74.6 % of children had viral load greater than 50,000virus/µL while 23.94% had CD4 counts <200. During the study period, 19.7% (14/71) of patients changed regimen, 85.7% of them were introduced to AZT while 14.3% included didanosine (ddl) in their combination. A single patient was changed to second line drugs.

Table 1: Characteristics of children starting ART

	Total	2004	2005	2006	2007	2008	2009
Number of children enrolled	71	7	20	21	9	12	2
Female, n (%)	35(49.3)	3(42.9)	7(35)	12(57.1)	7(77.8)	6(50)	0(0)
Age, Median (IQR)	5(2-7)	7(6-7)	5(1.25-1.75)	5(4-7)	3(1-6)	4(3.5-7.5)	6
≤18months, n (%)	6(8.8)	0(0)	1(16.7)	1(16.7)	3(50)	1(16.7)	0(0)
CD4 counts, Median (IQR)	358(203.25-)	207(83-522)	238(144-450.5)	509(356-652)	266(220-452)	391(284-584.5)	319.5(261.25-377.75)
Weight Median (IQR)	14.5(11-18.35)	16.5(15.7-18.625)	15.3(9.5-17.85)	13.7(11.375-18.475)	13.4(7.5-17)	12.9(11.6-15.625)	19.7(18.75-20.65)
WAZ Z score	-2.56(-4.12--1.6675)	-3.26(-5.315 -2.25)	-2.125(-3.645--1.695)	-2.63(-3.91--1.08)	-3.6(-4.06--2.9)	-2.66(-4.3425--1.65	-0.395(-1.0775-0.2875)
WAZ <-3 n(%)	26(36.62)	4(57.14)	5(25.00)	6(28.57)	6(66.67)	5(41.67)	0
Viral Load Median(IQR)	125673(58094-328424.5)	124860(108278-261377)	117703.5(35162-500000)	144272(13666-248162)	129048(121179-278948	90477(58643.5-282664)	177466(177466.5-17747.5)
Regimen n(%)							
d4T-3TC-EFV	51(71.8)	5(9.8)	13(25.5)	17(33.3)	5(9.8)	9(17.6)	2(3.9)
AZT-3TC-EFV	2(2.8)	2(100.0)					
d4T-3TC-NVP	4(5.6)		3(75.0))	1(25.0)			
d4T-3TC-LPV/r	10(14.1)		3(30.0)	1(10.0)	4(40.0)	2(20.0)	
AZT-3TC-NVP	1(1.4)			1(100.0)			
d4T-3TC-Kal	1(1.4)			1(100.0)			
Missing info	2(2.8)		1(50.0)			1(50.0)	

Table 2: Immunological, clinical and virological outcome of children on ART

	ART initiation (n=71)	**6wks (n=43)**	**3months (n=48)**	**6months (n=43)**	**12months (n=34)**	**18months (n=28)**	**24months (n=24)**	**30months (n=16)**	**36months (n=6)**	**42 months (n=2)**	**48 months (n=1)**
CD4 Median (IQR)	358(203.25-570.75)	639(337.5-1218)	750(462.25-1150.25)	863(432.5-1219)	856(483.5-1114.75)	905(571-1149)	1039.5(639.25-1166.25)	950(645.5-1097.25)	769.5(633-1131.75)	1323(1212.5-1433.5)	
Weight Median (IQR)	14.5(11-18.35)	16.3(12-18.95)	17.3(12.88-20.15)	18.0(13.48-21.08)	18.85(14.53-21.13)	20.25(17.2-23.8)	21.45(16.15-23.73)	23.7(21.45-25.85)	25.1(23.5-34.13)	31.5(28.1-34.9)	
WAZ Median (IQR	-2.56 (-4.12--1.6675	-2.34 (-3.41--1.24)	-1.89 (-2.535--1.045)	-2.015 (-2.9225--0.9925)	-2.09 (-2.72--1.115)	-2.115 (-2.66--1.2025)	-1.705 (-2.925--1.16)	-1.79 (-2.665--1.485)	-1.745 (-2.3925--1.4725)	-0.695 (-0.9725--0.4175)	-2.02
WAZ <-3 n(%)	26(36.62)	15(34.88)	8(16.67)	10(23.25)	10(29.41)	5(17.86)	5(20.83)	2(12.5)	0(0)	0(0)	0(0)
VL <50 n(%)	0 (0)	29(67.44)	30(62.50)	32(74.42)	24(70.59)	23(82.14)	19(79.17)	11(68.75)	5(83.33)	2(100)	1(100)

4.3 Immunological Outcome

The median CD4+ count increased from 358 cells/mm^3 (IQR 203.25-570.75) at ART initiation to 863 cells/mm^3 (IQR 432.5-1219) after six months of ART initiation then stayed more or less constant up to 30 months of follow-up (Table 2). On average, the CD4+ count increased over time (figure 1). The statistical analysis result shows that the covariate "Time" is a significant predictor of CD4+ values (p <0.0001). Time has a significant positive effect i.e. as time goes on, the CD4+ count increases. However, a significant (p<0.0001) negative relationship was observed between age and CD4 count when children ≤18 months and those >18 months were analyzed (Table 3). There was no difference in the trend of CD4 counts between male and female patients (p=0.6621).

Table 3: Solution for Fixed Effects – CD4

Effect	SEX	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		10.4981	1.2580	74.5	8.34	<.0001
month		0.7389	0.1113	306	6.64	<.0001
AGE		-0.8079	0.1296	95.2	-6.23	**<.0001**
SEX	**Female**	0.5260	1.1970	52.6	0.44	**0.6621**
SEX	**Male**	0	.	.	.	.
month*month		-0.03369	0.007284	303	-4.63	<.0001
month*month*month		0.000484	0.000125	302	3.88	0.0001

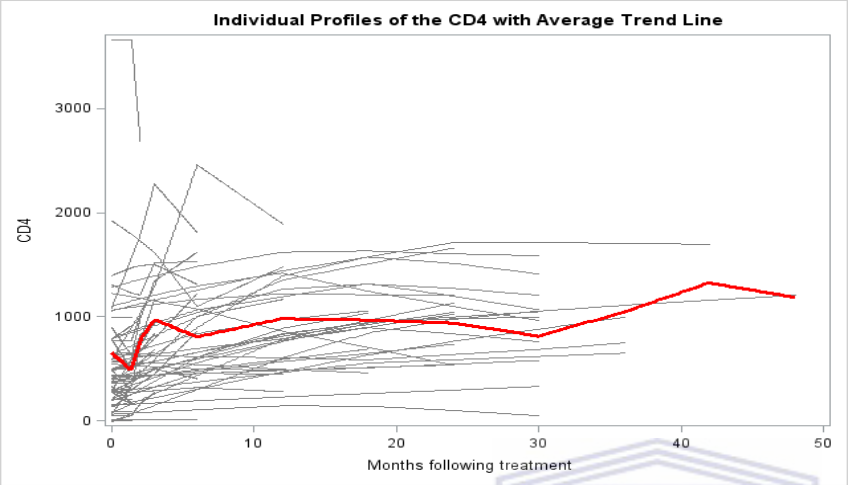

Figure 1: Individual profile of CD4 counts (cells/mm^3) for children on ART showing the average trend (red line).

4.4 Virological Outcome

Among the 71 children who started ART 59 (83.1%) had at least one follow-up viral load measurement. Among those who did not have any follow-up viral load measurement, 50% (6/12) died before their next (the six weeks) appointment. The median viral load at ART initiation was 125673 RNA copies/ml (IQR 58094-328424.5). After six weeks of starting ART, 67.44% of children experience viral suppression (<50 RNA copies/ml) and this proportion increased to 70.59% and 79.17% after one and two years respectively (Table 2).

The mean profile plot for viral load shows that viral load decreases as time increases (Figure 2). This is supported by the statistical analysis which shows a negative time effect (p <0.0001). As time increases the viral load decreases. There is also a significant age effect (p <0.0010) with viral load decreasing as age increases (Table 4). Like CD4 counts, there was no significant gender difference in the viral load trend (p=0.7516).

Table 4: Solution for Fixed Effects – Viral load						
Effect		**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		21.2840	2.0902	64.8	10.18	<.0001
month		-3.2504	0.3706	330	-8.77	<.0001
AGE		-0.7395	0.2137	53.9	-3.46	0.0011
SEX	**Female**	-0.5623	1.7651	42.2	-0.32	**0.7516**
SEX	**Male**	0	.	.	.	.
month*month		0.1718	0.02434	324	7.06	<.0001
month*month*month		-0.00248	0.000417	325	-5.94	<.0001

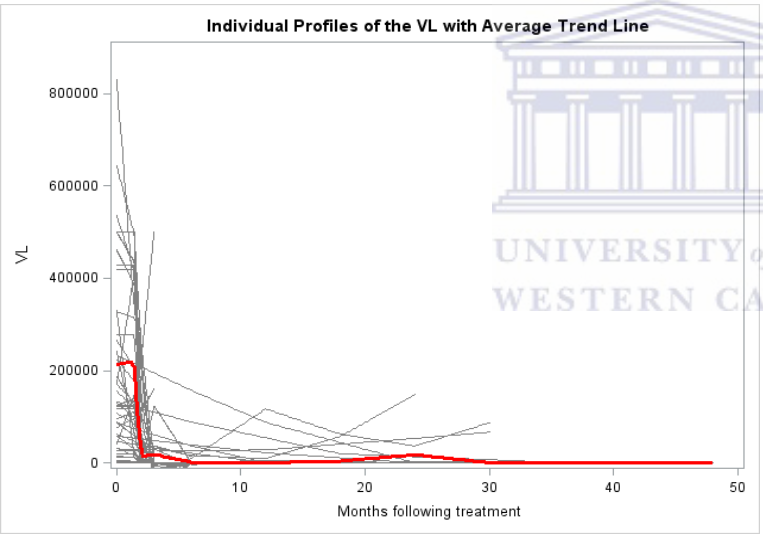

Figure 2: Individual viral load (RNA copies/ml) profile for children on ARTs showing average trend (in red)

4.5 Clinical Outcome

The mean profile plot for WAZ score shows that weight-for-age for children on ART increased within the first three months and remained steady over a period of two years before showing an increase (figure 3). The median weight of children at ART initiation was 14.5Kg (IQR 11.0-18.35)

increasing to 18Kg (IQR 13.48-21.08) after six months of treatment and 18.85 (IQR 14.53-21.13) after one year of follow-up (Table 2). The median weight-for-age within this period was -2.56 (IQR -4.12 - -1.6675), -2.015 (IQR -2.9225 - -0.9925) and -2.09 (IQR -2.7 - -1.115) respectively. The statistical result shows that the covariates "Time" and "Age" are significant predictors of weight (p <0.0001 and p<0.0001 respectively). Time has a significant positive effect i.e. as time goes on, the weight also increases.

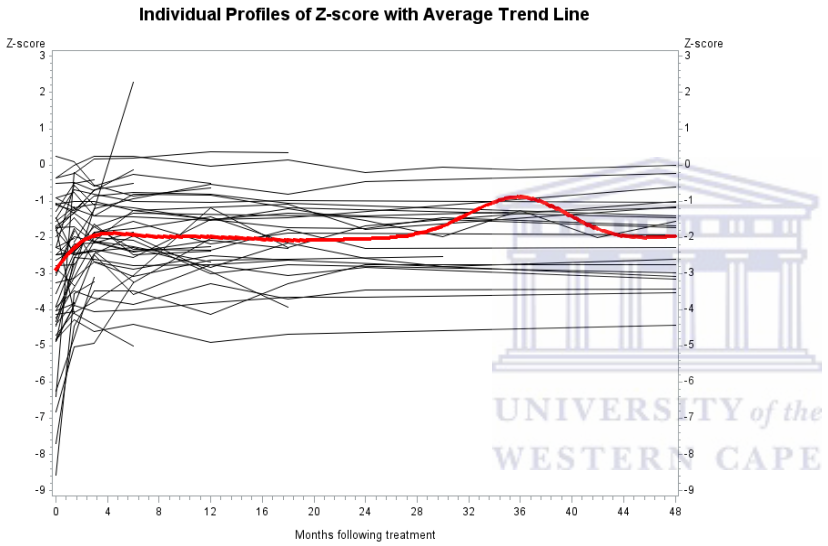

Figure 3: Individual weight profile of children on ARTs at initiation time and follow-up period showing average trend

4.6 Transfers, mortality and loss to follow-up

Within the study period, three children (4.23%) grew out of the children group and were transferred to adult group while some patients (7.04%) moved from Bela-Bela to another town or even province. Nineteen percent (14/71) of patients died during the study period and 21.43% of these were children who were 18 months or less (Table 5). Mortality was the same for male and female with all patients

dying within the first year of ART initiation. Ninety two percent of those who died had viral loads >50,000 while 72.4% had CD4 counts less than 350 cells/mm^3 at the time they commenced ART.

Five children (7.04%) were lost to follow-up and their files closed due to non-adherence. All five patients were lost to follow-up within two years of ART initiation with only one of them receiving treatment for up to two years. After experiencing virological suppression, children were referred to PHC where they continued treatment. Most of the children were transferred to PHC at the end of 2009 and as shown on table 3 by the end of 2009, 33 children (46.5% of the 71 who started ART at the clinic) moved to PHC, 25 (75.8%) of them are still receiving treatment as at August 2012. Two children died at PHC while 4 have been lost to follow-up (Table 5). 10 (14.08%) children are still receiving treatment at the HAPG clinic.

Table 5: Summary of cohort of children who initiated treatment at the HAPG clinic in Bela-Bela after four years of follow-up

Number starting ART at clinic n (%)	**71**
Still on ART at clinic	10(14.08)
Died on ART at clinic	14(19.72)
LTFU (non adherence)	5(7.04)
Transferred (other town or province)	5(7.04)
To adult group	3(4.23)
referred to PHC(still on treatment)	25(35.21)
referred to PHC died on ART	2(2.82)
referred to PHC LTFU	4(5.63)
referred to PHC transferred	2(2.82)

4.7 Survival Analysis

Not including the 14 children who died, 57 observations were censored. In Kaplan-Meier analysis CD4 count at ART initiation was a significant univariate predictor of death (p=0.0206), and age less than 18 months (p=0.1235) was a univariate predictor by Cox proportional hazards modeling (CPHM) (Table 4a). Kaplan-Meier (K-M) survivor curve for CD4 count at time of initiating ART (Figure 4) shows that there is a difference in survival between those with higher CD4 (>358cells/mm^3) and those with lower CD4+ count (<358 cells/mm^3). The higher K-M curve for those with higher CD4+ group suggests that this group has a higher chance of long term survival. A log-rank test statistic value of 5.4 confirms this difference with an approximate p-value of 0.0206. The multivariate CPHM shows that age and baseline CD4+ are significant predictors of survival duration (Table 4a).

Table 6a: Analysis of Maximum Likelihood Estimates (full model)

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
AGE		1	-0.27362	0.12043	5.1622	0.0231	0.761	
vl_cat	**0**	1	-0.57593	0.77391	0.5538	0.4568	0.562	Rank for Variable VL 0
SEX	**Female**	1	0.57314	0.76066	0.5677	0.4512	1.774	SEX Female
cd4_cat	**0**	1	2.27552	0.93589	5.9117	0.0150	9.733	Rank for Variable CD4 0

Table 6b: Analysis of Maximum Likelihood Estimates (reduced model)

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
AGE		1	-0.28217	0.11061	6.5072	0.0107	0.754	
cd4_cat	**0**	1	**2.27124**	0.86414	6.9081	**0.0086**	9.691	Rank for Variable CD4 0

Here it is confirmed again that there is a significant difference between the two baseline CD4+ groups (0=CD4+ <358, 1=CD4+>358cells/mm^3). The estimated coefficient for CD4 group is 2.3 with p-value 0.0086 (Table 6b). Hence, with other covariates fixed, baseline CD4+ group 0 have an increased hazard, and, hence, have shorter expected survival time than those in Group 1. Fixing other covariates, the hazard ratio between Group 0 and Group 1 is 9.7. This means that, with other

covariates fixed, patients with Initial CD4+ group 0 are 9.7 times more likely than baseline CD4+ group 1 to have shorter survival. The estimated coefficient for age is -0.2822 with p -value 0.0107 (Table 6b). Hence, fixing other covariates, older children have a decreased hazard, and, hence, have longer expected survival time than younger children.

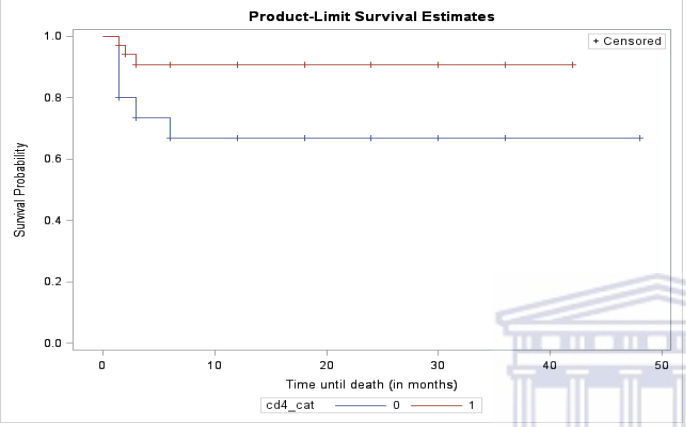

Figure 4: Probability of patient survival as predicted by CD4 count at ART initiation. 0 = CD4 count <361 cells/mm^3, 1 = CD4 count > 361 cells/mm^3 children less than 18months, 1 = children > 18 months

Viral load (p=0.4568) and sex (p=0.4512) were not significant predictors of death (Table 6a). There was no significant difference in survival between male and female patients.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Discussion

HIV in children initially did not attract as much attention as it did with adults but in recent years, paediatric HIV has become an increased priority due to its devastating effects on children and young adults. In South Africa, a significant number of children die from HIV and more are being infected and still live with the disease. In the words of the South African Department of Health report, "children usually do not have sufficient access to AIDS treatment and care because available services are mostly designed for adults" (DoH, 2009).

With South Africa having the largest ART program in the world and at the same time seeking ways to increase and improve access for the large number of HIV/AIDS patients in the country, it is essential that key outcomes be understood that will help in planning for the changing needs of patients, planners and provider services. In most industrialized countries, HIV treatment is individualized while in low- and middle-income countries, ART programmes follow WHO developed recommendations due to lack of or limited resources in the health systems in these countries. These ART programs have been shown to be as effective as those of the individualized programs (Sutcliffe *et al*, 2008; Keiser *et al*, 2008).

This study looked at the outcome of the ART program of a peri-urban town in the Limpopo Province of South Africa. It described the characteristics of children in this program at ART initiation and the long term outcome of the treatment program. Parameters that have been used to assess the outcome of treatment programs include CD4 counts (immunological), viral load (virological), weight (clinical), mortality and loss to follow-up. After an initial six weeks and three months monitoring of patients, a

six monthly virological, immunological and clinical monitoring was performed for each child in the cohort. Based on these parameters, the findings of this study demonstrate good outcomes for children receiving treatment at the HAPG clinic and suggest that positive outcomes are possible in low and middle- income settings.

As shown in Table 2, the median CD4 level was more than double the baseline level after six months of follow up. This is in line with many similar studies that have shown positive outcomes for children on ART (Davis *et al*, 2009; Cohen *et al*, 2009; Bolton-Moore *et al*, 2007). CD4 is the most common measurement of disease severity and staging in HIV positive patients particularly in the absence of viral RNA testing. Even in the presence of viral load testing, CD4 counts and percentage is important in determining how well a patient can be able to fight other infections. With children predisposed to other bacterial and fungal infections in the face of HIV, an improvement in their CD4 counts would mean improved ability to fight opportunistic infections.

A similar trend as CD4 was observed for weight with the median weight for age z scores of children in this cohort showing an improvement within two years of follow up (Table 2). Improvement in weights and appropriate growth in a child is an indication that malnutrition decreased during treatment. Although there were some cases of children who were underweight for their age (z score <-3) within the study period, overall, children's growth was within acceptable range as measured by WAZ. The nutritional status of HIV infected children has been shown to correlate with their immunological and virological status with a negative correlation observed between viral load and certain nutritional indicators (Steenkamp *et al*, 2009). Poor nutrition compromises the immune function of children thereby predisposing them to infections. In this cohort, good clinical outcome was matched by improved immunological and virological outcomes (Table 2).

A decline in viral load was observed during the period of this study (Table 2, Fig 2). Virological suppression was observed in more than 70% of children after one year on treatment. This outcome is comparable to similar smaller and larger studies that have been carried out in Sub-Saharan Africa (Sutcliffe *et al*, 2008). The availability of viral load testing was of great advantage in this cohort since virological data could be compared with immunological information to aid in treatment decision. In many low and middle income settings, viral RNA determination is rare and as such, treatment is based mainly on CD4 level alone making it difficult to be able to determine treatment failure, viral rebound and when to switch to other treatment options. Change in treatment for children in the HAPG clinic was based on both viral load and CD4 information.

The aim of antiretroviral treatment is to reduce viral load to levels that may not cause illness and cannot be transmitted. Like with adult patients, children require a combination of at least three drugs in order to achieve viral suppression. The recommended combinations usually include two nucleoside reverse transcriptase inhibitors (NRTI) and either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. For infants, NVP and two NRTI is recommended for those who were never exposed to ART and for infants whose exposures cannot be determined. Lopinavir/ritonavir replaces NVP for children exposed to NVP or other NNRTI (WHO, 2010b). In this study Lamivudine (100%) and Stavudine (92.9%) were the most common NRTI backbone used. This is in line with the WHO recommendation for infants and children. Ten patients had the LPV/r combination pointing to the fact that ten children were exposed to ART either through the mother or as an infant during the early days of live. Although LPV/r has been demonstrated to cause viral suppression in children, it is however cautioned that its palatability and possible interactions be taken into consideration before using LPV/r based drugs for first line therapy (Meyer *et al*, 2012).

Stavudine was one of the NRTI used in 92.9% of patients in this study. This drug has been associated with toxicity resulting in its substitution in some patients. In this study, Stavudine was replaced with Zidovudine in patients who experienced lactic acidosis (either mild moderate or severe) and those with hyperlactataemia. Treatment failure was also observed in some patients and either Didanosine (ddl) or Zidovudine was a replacement of choice. Despite its known toxicity which in some cases may result in its replacement in some treatment combinations, Stavudine is still a safe and effective option for children in situations where treatment options are limited (Palmer *et al*, 2012).

Some adult studies have shown gender associations in HIV treatment outcomes (Cornell *et al*, 2012; Collazos et al, 2007; Chen et al, 2008) while others did not (Nicastri *et al*, 2007). In this study, however, there was no significant difference in the trends observed for viral load (p=0.7516), CD4 counts (p=0.6621) and weight between male and female patients.

Loss to follow-up during the study period was 7.04% which compares with some earlier studies that were done in some Sub-Saharan countries (Sutcliffe *et al*, 2008). It has been observed that loss to follow-up in paediatric ART has not increased in recent years with high numbers observed mostly in bigger facilities that are burdened with large patient loads (Fatti *et al*, 2011). In such situations, it is difficult to keep track of every single patient given the limited resources, particularly human resources. The HAPG clinic is located in a peri-urban town and patients (adults and children) are monitored on a regularly basis including home visits by members of the group and community workers.

By the end of 2009, more than 65% of children were still on treatment and only a single patient switched to second line regimen (usually an indication of treatment failure probably due to virus resistance to initial drugs). Although AZT was introduced in some patients, the fact that only a single

patient switched to second line treatment points to the ability of patients to adhere to their treatment and therefore minimize the selection of resistant viruses. Development of resistance has been associated with the lack of proper viral load monitoring, drug interaction, poor adherence and/or drug interruption due to non-availability of drugs and the use of substandard dose of antiretroviral drugs which may lead to virus selection of resistant mutations (Hamers *et al*, 2012). Change of regimen for children in this cohort was due to development of conditions such as mild or moderate lactic acidosis (35.7%), hyperlactaemia (28.5%) and treatment failure which could be associated with resistance (35.7%). On the other hand, the low number of children switching treatment may point to the fact that care providers may be concentrating more on adherence counseling and failing to see the need for treatment change in the face of virological failure.

Early mortality in treatment has been reported in many ARTs programs particularly for children less than 18 months (Meyers *et al*, 2011; Fatti *et al*, 2008). In this study, mortality was recorded within the first year of treatment initiation with most children (71.43%) dying within 90 days of treatment. This was probably due to the advanced disease stage of the patients since most of the patients who died on treatment had CD4 <350 cell/µL and viral load >50,000copies of RNA. Similar results have been obtained in other cohort studies (Meyer *et al*, 2012; Barth *et al*, 20011; Boulle *et al*, 2008) with direct correlation between mortality and low CD4% and low weight for age at the time treatment was initiated. The high proportion (42%) of children less the 18 months who died may reflect the fact that diagnosis was not prompt and children were not able to access treatment on time. WHO recommends ART initiation in infants and young children irrespective of disease stage or CD4 count. However, not all settings are well resourced to follow these recommendations and as such, treatment in many cases follow the disease stage system. The WHO 2008 recommendation was adopted in South Africa two years after it was published thus treatment of children in this cohort did not follow the revised South

African guidelines. Treatment was provided to all patients (children and adults) with CD4≤200 cell/μL and at stage IV of the disease. Immune reconstitution inflammatory syndrome (IRIS), did not account for the high mortality experienced in patients in this cohort. IRIS is an illness that occurs in a small proportion of patients soon after ART commencement due to a rapid response of the immune system to opportunistic infections, which were initially present in the patient, but were dormant and asymptomatic. The symptoms of IRIS are normally mild, but may be life threatening in certain cases, with patients starting ART when the immune system is severely damaged being at higher risk of developing IRIS (Muller et al, 2010). Four children developed tuberculosis (TB) and were treated. None of the TB patients died on ART. Non-tubercular mycobacterium was not seen in any of the patients.

5.2 Study Limitations

Since data was collected retrospectively, all relevant information was not available and some of the available data were incomplete. In addition, errors in recording some information and bias due to unmeasured determinants cannot be ruled out.

5.3 Conclusion

The overall findings of this study are similar to other studies that have been conducted in both urban and rural settings and points to the need for regular program evaluation to determine the ever changing need of HIV infected children in a country that has a high burden of the disease. The study shows good outcomes for children in the program but recorded a high mortality occurring within the first year of treatment initiation. This suggests the need for early diagnosis and early initiation of treatment particularly in children less than 18 months. Although the program recorded a more than 70% patient

retention, more efforts need to go into dealing with adherence and in this light, home visits and community support need to be strengthened.

5.4 Recommendations

With more than 90% of children being infected through MTCT, a programme that will help reduce MTCT will be the most effective way to fight paediatric HIV worldwide. While the HAPG programme shows good outcome for children, there is still a need for improvement to attain better outcomes. The high mortality at early age and within 90 days of ART initiation highlights the need for early identification/diagnosis of infected and exposed children and early initiation of treatment. This can be achieved by promoting VCT through integration of maternal and child health programmes. Since the children in this cohort started treatment before South Africa adopted the current WHO guidelines, it is recommended that the programme follows the recent guidelines for future children that enroll at the clinic.

LTFU and poor adherence has been observed in many ART programmes in Africa and adherence to a greater extent determines the efficacy and durability of ART regimen. In this light, a system of adherence counseling and monitoring be put into place to help patients follow their treatment accordingly. It will also be beneficial to qualitatively research on non-adherence to determine reasons why some patients are unable to follow their treatment and therefore design programme to address such.

WHO recommends that each child receives treatment irrespective of CD4 counts and disease stage, however, different settings and provinces have different challenges in paediatric ART delivery. In this respect, the Government should set out national standards but at the same time research the needs of low income settings and work towards addressing such needs. It is also recommended that a provincial and regional prevalence be determined in order to access whether the proportion accessing treatment reflects the expected proportion that is infected.

There is always the need for human resources in the delivery of ART, both adult and paediatric. A programme to train more counselors and community workers is of the essence in the general fight against HIV/AIDS.

REFERENCES

Atashili, J., Poole, C., Ndumbe, P. M., Adimora, A. A. and Smith J. S. (2008). Bacterial vaginosis and HIV acquisition: a meta-analysis of published studies. *AIDS*, 22: 1493-1501

Barth, R. E., Tempelman, H. A., Moraba, R. and Hoepelman, A. I. M. (2011). Long term outcome of an HIV-treatment programme in rural Africa: Viral suppression despite early mortality. *AIDS Research and Treatment*, 2011:1-5

Barth, R. E., Tempelman, H. A., Smelt, E., Wensing, A. M. J., Hoepelman, A. I. and Geelen, S. P. (2010). Long term outcome of children receiving antiretroviral treatment in rural South Africa: Substantial virologic failure on first-line treatment. *Pediatric Infectious Disease Journal*, 30: 53-56.

Becquet, R., Marston, M., Dabis, F., Moulton, L. H., Gray, G., Coovadia, H. M., Essex, M., Ekouevi, D. K., Jackson, D., Coutsoudis, A., Kilewo, C., Leroy, V., Wiktor, S. Z., Nduati, R., Msellati, P., Zaba, B., Ghys, P. D., Newell, M-L. and the UNAIDS Child survival group (2012). Children Who Acquire HIV Infection Perinatally Are at Higher Risk of Early Death than Those Acquiring Infection through Breastmilk: A Meta-Analysis. *PLoS ONE*, 7(2): e28510

Bolton-Moore, C., Mubiana-Mbewe, M., CantrellR. A., Chintu, N., Stringer, E. M., Chi, B. H., Sinkala, M., KankasaC., Wilson, C. M., Wilfert, C. M., Mwango, A., Levy, J., Abrams, E. J., Bulterys, M. and Stringer, J. S. A. (2007). Clinical Outcomes and CD4 Cell Response in Children Receiving Antiretroviral Therapy at Primary Health Care Facilities in Zambia. *JAMA*, 298(16): 1888-1899

Boulle, **A.**, Bock, P., Osler, M., Cohen, K., Channing, L., Hilderbrand, K., Mothibi, E., Zweigenthal, V., Slingers, N., Cloete, K. and Abdullah, F. (2008) Antiretroviral therapy and early mortality in South Africa. *Bulletin of the World Health Organization*, 86(9): 678–687.

Buchbinder, S. P., Mehrotra, D. V., Duerr, A., Fitzgerald, D. W., Mogg, R., Li, D., Gilbert, P. B., Lama, J. R., Marmor, M,, Del Rio, C., McElrath, M. J., Casimiro, D. R., Gottesdiener, K. M., Chodakewitz, J. A., Corey, L. and Robertson, M. N., Step Study Protocol Team. (2008). Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*, 372(9653):1881-93.

Campbell, C. (2010). Political will, traditional leaders and the fight against HIV/AIDS: a South African case study. *AIDS Care* 00:1-7

Chen, S. C., Yu, J. K., Harries, A. D., Bong, C. N., Kolola-Dzimadzi, R., Tok, T. S., King, C. C. and Wang, J. D. (2008). Increased mortality of male adults with AIDS related to poor compliance to antiretroviral therapy in Malawi. *Trop Med Int Health.*, 13(4):513-9

Chopra, M., Doherty, T., Goga, A., Jackson D. and Persson, L. A. (2010). Survival of infants in the context of prevention of mother to child HIV transmission in South Africa. *Acta Paediatrica*, 99(694-698).

Cohen, D. A., Wu, S. Y. and Farley T. A. (2004). Comparing the cost-effectiveness of HIV prevention interventions. *J Acquir Immune Defic Syndr*, 37(3):1404-14

Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., Hakim, J. G., Kumwenda, J., Grinsztejn, B., Pilotto, J. H., Godbole, S. V., Mehendale, S., Chariyalertsak, S., Santos, B. R., Mayer, K. H., Hoffman, I. F., Eshleman, S. H., Piwowar-Manning, E., Wang, L., Makhema, J., Mills, L. A., de Bruyn, G., Sanne, I., Eron, J., Gallant, J., Havlir, D., Swindells, S., Ribaudo, H., Elharrar, V., Burns, D., Taha, T. E., Nielsen-Saines, K., Celentano, D., Essex, M. and Fleming, T. R; HPTN 052 Study Team. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*, 365(6):493-505.

Cohen, R., Lynch, S., Bygrave, H., Eggers, E., Vlahakis, N., Hilderbrand, K., Knight, L., Pillay, P., Saranchuk, P., Goemaere, E., Makakole, L. and Nathan Ford. (2009). Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years. *Journal of the International AIDS Society*, 12:23

Collazos, J., Asensi, V. and Cart J. A. (2007). Sex differences in the clinical, immunological and virological parameters of HIVinfected patients treated with HAART. *AIDS*, 21(7): 835-843

Cornell, M., Schomaker, M., Garone, D. B., Giddy, J., Hoffmann, C. J., Lessells, R., Maskew, M., Prozesky, H., Wood, R., Johnson, L. F., Egger, M., Boulle, A., Myer, L.; for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration (2012). Gender Differences in Survival among Adult Patients Starting Antiretroviral Therapy in South Africa: A Multicentre Cohort Study. *PLoS Med*, 9(9):e1001304

.

Davies, M-A., Keisa, O., Technau, K., Eley, B., Rabie, H., van Cutsem, G., Giddy, J., Wood, R., Boulle, A., Egger, M., Moultrie, H., for the International epidemiology Database to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration. (2009). Outcome of the South African national antiretroviral treatment programme for children: The IeDEA Southern Africa collaboration. *South African Medical Journal*, 99(10): 730-737.

DeGruttola, V., Smith, D. M., Little, S. J. and Miller, V. (2010). Developing and Evaluating Comprehensive HIV Infection Control Strategies: Issues and Challenges. *Clin Infect Dis*, 50(Suppl 3):S102-7

De Koker, P., Lefevre, P., Matthys, F., van der Stuyft, P. and Delva, W. (2010). Barriers to VCT despite 13 years of community-based awareness campaigns in a peri-urban township in northern Limpop. *South African Medical Journal*, 100(6): 364-365.

Department of Health. (2009). Access to antiretroviral treatment in children. HIV & AIDS and STI *National Strategic Plan 2007-2011*, page 1-4.

Department of Health. (2010). Policy and Guidelines for the Implementation of the PMTCT Program. South Africa.

Department of Health (2011). The 2010 National Antenatal Sentinel HIV & Syphilis Prevalence Survey in South Africa.

Dlodlo, R. A., Fujiwara, P. I., Hwalima, Z. E., Mungofa, S. and Harries, A. D. (2011). Adult mortality in the cities of Bulawayo and Harare, Zimbabwe: 1979–2008. *J Int AIDS Soc* 14 Suppl 1:S2-S9.

Euser, A. M., Zoccali, C., Jager, K. J. and Dekker, F. W. (2009). Cohort studies: prospective versus retrospective. *Nephron Clin Pract*, 113:c214–c217

Fatti, G., Bock, P., Eley, B., Mothibi, E. and Grimwood, A. Temporal Trends in Baseline Characteristics and Treatment Outcomes of Children Starting Antiretroviral Treatment: An Analysis in Four Provinces in South Africa, 2004–2009. *J Acquir Immune Defic Syndr*, 58(3): e60-67

Fennel, L. (2010). Early mortality and loss to follow-up in HIV-infected children starting antiretroviral therapy in Southern Africa. *J Acquir Immune Defic Syndr*. 2010 54(5): 524-32

Hamers, R. L., Sigaloff, K. C., Kityo, C., Mugyenyi, P, and de Wit T. F. (2012). Emerging HIV-1 drug resistance after roll-out of antiretroviral therapy in sub-Saharan Africa. *Curr Opin HIV AIDS* [Epub ahead of print

Ingle, S. M., May, M., Uebel, K., Timmerman, V., Kotze, E., Bachmann, M., Sterne, J. A., Egger, M., Fairall, L.and IeDEA-SA. (2010). Differences in access and patient outcomes across antiretroviral treatment clinics in the Free State province: a prospective cohort study. *Afr Med J*. 100(10):675-81

Jahn, A., Floyd, S., Crampin, A. C., Mwaungulu, F., Mvula, H., Munthali, F., McGrath, N., Mwafilaso, J., Mwinuka, V., Mangongo, B., Fine, P. E., Zaba, B. and Glynn, J. R. (2008). Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet*, 371:1603–1611

Janssen, N., Ndirangu, J., Newell, M. L. and Bland, R. M. (2009). Successful paediatric HIV treatment in rural primary care in Africa. *AIDS Review*, 11(4): 179-89.

Johnson, W. D., Diaz, R. M., Flanders, W. D., Goodman, M., Hill, A. N., Holtgrave, D., Malow, R. and McClellan, W. M. (2008). Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. *Cochrane Database Syst Rev*, CD001230.

Keiser, O., Orrell, C., Egger, M., Wood, R., Brinkhof, M. W., Furrer, H., van Cutsem, G., Ledergerber, B., Boulle, A., Swiss HIV Cohort Study (SHCS) and the International Epidemiologic Databases to Evaluate AIDS in Southern Africa (IeDEA-SA). (2008) Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS Med*, 5(7):e148.

.Kesho Bora Study Group. (2011). Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *The Lancet Infectious Diseases*, **11(3)**: 171 – 180

Klasse P. J., Shattock, R. J. and Moore, J. P. (2006). Which topical microbicides for blocking HIV-1 transmission will work in the real world. *PLoS Med,* 3(9): 1501-1507

Mmbaga, E. J., Leyna, G. H., Stray-Pedersen, B. and Klepp, K. I. (2011). Herpes simplex virus type-2 and human immunodeficiency virus infections in a rural population in Kilimanjaro Tanzania. *East Afr J Public Health,* 8(1):28-32.

Meyers, T., Yotebieng, M., Kuhn, L. and. Moultrie, H. (2011). Antiretroviral therapy response among children attending a large public clinic in Soweto, South Africa. *Paediatr Infect Dis J*., 30(11): 974–979

Field Code Changed

Müller, M., Wandel, S., Colebunders, R., Attia, S., Furrer, H., Egger, M., IeDEA Southern and Central Africa. (2010). Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*, 10(4): 251-261

Ndjeka, N. O. and Manhaeve, C. (2006). The experience of the Bela Bela HIV prevention group with the roll out of antiretroviral therapy at the primary health care level. *South Africa Family Practice*, 48(4): 56-57.

Nicastri, E., Leone, S., Angeletti, C., Palmisano, L., Sarmati, L., Chiesi, A., Geraci, A., Vella, S., Narciso, P., Corpolongo, A. and Andreoni, M. (2007). Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. *J Antimicrob Chemother*, 60(4):724-32

Palmer, M; Chersich, M; Moultrie, H; Kuhn, L; Fairlie, L. and Meyers, T. (2012). Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in Soweto, South Africa. *AIDS*, Epub ahead of print.

Paintsil, E. (2010). Monitoring antiretroviral therapy in HIV-infected children in resource-limited countries: A tale of two epidemics. *AIDS Research and Treatment*, 2011: 1-9.

Raguenaud, M-E., Isaakidis, P., Zachariah, R., Te, V., Soeung, S., Akao, K. and Kumar, V. (2009). Excellent outcomes among HIV+ children on ART, but unacceptably high pre-ART mortality and losses to follow-up: a cohort study from Cambodia. *BMC Pediatrics*, 9:54

Reniers, G., Araya, T., Davey, G., Nagelkerke, N., Berhane, Y., Coutinho, R. and Sanders, E. J. (2009). Steep declines in populationlevel AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa. *AIDS*, 23:511–518.

Rerks-Ngarm, S., Pitisuttithum, P., Nitayaphan, S., Kaewkungwal, J., Chiu, J., Paris, R., Premsri, N., Namwat, C., de Souza, M., Adams, E., Benenson, M., Gurunathan, S., Tartaglia, J., McNeil, J. G., Francis, D. P., Stablein, D., Birx, D. L., Chunsuttiwat, S., Khamboonruang, C., Thongcharoen, P., Robb, M. L, Michael, N. L., Kunasol, P., Kim, J. H., MOPH-TAVEG Investigators. (2009). Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*, 361:2209-2220.

Steenkamp, L., Dannhauser, A., Walsh, D., Joubert, G., Veldman, F. J., Van der Walt, E., Cox, C., Hendricks, M. K. and Dippenaar, H (2009). Nutritional, immune, micronutrient and health status of HIV-infected children in care centres in Mangaung. *S Afr J Clin Nutr*, 22(3):131-136

Sutcliffe, C. G., Bolton-Moore, C., van Dijk, J. H., Cotham, M., Tambatamba, B. and Moss, W. J. (2010). Secular trends in pediatric antiretroviral treatment programs in rural and urban Zambia: a retrospective cohort study. *BMC Pediatrics*, 10:54

Sutcliffe, C. G., van Dijk, J. H., Bolton-Moore, C., Persuad, D. and Moss, W. J. (2008). Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa. *The Lancet Infectious Disease*, 8: 477-489.

UNAIDS (2011). World AIDS day report

UNAIDS (2011). Global HIV/AIDS Response: Epidemic Update and Health Sector Progress Towards Universal Access. Progress report 2011.

UNAIDS 2010. Report on the global AIDS epidemic

UNICEF. (2010). Monitoring the situation of children and women. [Online], Available: http://www.childinfo.org/hiv_aids_treatment_care.html?q=printme [Downloaded: 15/02/2011]

World Health Organization (2012) HIV/AIDS Fact sheet No 360.

WHO, UNAIDS and UNICEF (2011) Global HIV/AIDS Response: Epidemic update and health sector progress towards universal access, Progress Report 2011.

World Health Organization. (2006a). Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach. [Online], Available: http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf [Downloaded: 11/04/2011]

WHO (2006b). Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access

World Health Organization. Revision (2010a). Antiretroviral therapy of HIV infection in infants and children: towards a universal access. Recommendations for a public health approach. [Online], Available: http://www.who.int/hiv/pub/guidelines/art/index.html [Downloaded: 25/02/2011].

World Health Organization (WHO). Progress report (2010b). Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector. [Online], Available: http://www.who.int/hiv/pub/2010progressreport/en/index.html [Downloaded: 25/02/2011].

World Health Organization. (2010c). PMTCT strategic vision 2010–2015 : preventing mother-to-child transmission of HIV to reach the UNGASS and Millennium Development Goals. [Online], Available: http://www.who.int/hiv/pub/mtct/strategic_vision.pdf [Downloaded: 15/11/2012].

World Health Organization Report. (2008) on the global HIV/AIDS epidemic. UNAIDS/WHO: Geneva, Switzerland.

World Health Organization. (2007). Prevention of Mother-To-Child Transmission (PMTCT). Briefing Note. [Online], Available: http://www.who.int/hiv/pub/toolkits/PMTCT%20HIV%20Dept%20brief%20Oct%2007.pdf [Downloaded: 15/11/2012].

WHO, UNICEF, UNAIDS (2008.). Towards Universal Access: scaling up priority HIV/AIDS interventions in the health sector. [Online], Available: http://www.who.int/hiv/mediacentre/2008progressreport/en/index.html [Downloaded: 01/03/2011].

APPENDICES

Appendix 1: Patient information recorded at baseline and at every follow-up after initiation of treatment

Patient No

Date of birth

Age

Sex

Weight

Height

WHO stage

CD4 count

Viral load

Treatment (drug type)

Treatment change? (Yes/No). If yes, New treatment

Other infections associated with HIV

Referred?

Appendix 2: Letter of permission from the HAPG

P.O.Box 177 – BelaBela 0480 – South Africa
Tambo Drive 1763 – BelaBela 0480
Community Coordination Centre
Phone 014 737 8196 – Cell 082 858 1277
Fax 014 737 8196 –email:thusanan@esnet.co.za
hivbela@esnet.co.za
NPO Registration 033 - 419

HIV/AIDS PREVENTION Group

To the UNIVERSITY OF VENDA
THOHOYANDOU

BelaBela, 04.10.2011

Dear Sirs,

Re: permission to use data from the HIV/AIDS Prevention Group, BelaBela.

On behalf of the Board of Directors and the Management Committee of the above mentioned organisation, I, Cecile Manhaeve. Director, hereby give permission to the Department of Microbiology, University of Venda, to make use of the data forwarded for research purposes.

We would appreciate it if we could be supplied with copies of the research findings.

Yours faithfully,

Cecile Manhaeve
Director

Funded by: Oxfam Community Aid Abroad Australia – Johap (Joint Oxfam) Durban –Catholic Relief Services – Firelight Foundation USA – Department of Welfare, Limpopo Province – S.A. Catholic Bishops Conference – Department of Health, Limpopo Province