# Paediatric Antiretroviral HIV Treatment: Measurement and correlates of adherence in a resource-poor setting.

**Desireé Michaels**
**MCHDES001**



**Thesis presented for the Degree of Doctor of Philosophy**
**in the Department of Public Health and Family Medicine**
**University of Cape Town**

**February 2008**

**Supervisor: Professor Leslie London**
**Co-supervisor: A/Professor Brian Eley**

# DECLARATION

I declare that this thesis is my own work. This work has not been previously submitted in whole, or part, for any award of any degree. Each significant contribution to, and quotation in this dissertation from the work, or works, of other people has been attributed and has been cited and referenced.

**Date: _____**

**Place: University of Cape Town**

**Signed:_____**

# ACKNOWLEDGEMENTS

Many people have contributed in various ways to the completion of this dissertation.

First, I would like to express my gratitude to Professor Leslie London who agreed to supervise the thesis when it was just an idea. He has been a source of encouragement and inspiration. I will always be grateful for your acknowledgement through your nomination for the Research Associate award granted to me in 2006. Thank you for the objective and diligent guidance throughout the process of writing this dissertation.

Associate Professor Brian Eley, who agreed that the research be conducted at the Infectious Diseases Clinic as well as being the co-supervisor for the thesis. Thank you for providing the paediatric HIV expertise, your input and support throughout this process is greatly appreciated.

Professor Gregory Hussey, for mentorship in the progress towards this doctorate degree (long before registration) and for allowing access to research staff and resources until the end. I will always be grateful for your role as my mentor in paediatric HIV, research and my academic career.

To Dr David Coetzee, for giving me the impetus to pursue this research by offering me a position in the unit and thus financial support for the major part of the research. Thank you for your input during protocol development and assistance in my search for grants.

To my ex-colleagues in the Infectious Disease and Epidemiology Unit, UCT: Dr Landon Myers for being the sounding board for my ideas in protocol design and his coaching in STATA; Dr Andrew Boulle for the many hours of design and setting up of the final database as well as the transformation of the database for analysis. I am most grateful for his encouragement and support throughout the study. To Dr Mary-Anne Davies, who shared her experience and information regarding her own adherence study and for providing comments on the analyses. To Mr Nkosinathi Sodladla for being there at the very beginning and willing to assist me without extra

remuneration by conducting the first interviews and assisting with the setting up of the research project including the Xhosa translations. I will always be grateful for your support.

To Wola Nani, thank you for the secondment of Nomandla Odogwu to work with me on this project. I would like to thank Nomandla, for her diligence and staying till the end of the study. To the other Wola Nani counselors based at Red Cross Hospital who were always willing to assist with identification of patients for recruitment.

To all the doctors and nurses based in Ward S4 especially Bonny Diener, Sr Spasina King, Sr Louise Laisai, and Dr Rupesh Daya who allowed me into their space and Sr Patti Appolles for access to information. A very special thank you to Sr Mackie Prins for direct involvement and practical assistance with study logistics (obtaining patient laboratory results, patient folders for review) and providing access to resources. I am most grateful.

For the people who coached me in the use of STATA: Lesley Workman (Bambi) for providing an overview of STATA capabilities and thus convincing me to switch over to STATA, Rosslyn Baaitjies for giving of her time generously and teaching me ungrudgingly even when she didn't really have the time and didn't even know me. Her patience and self-sacrifice meant so much to me.

To Dr Francesca Little for her time in discussing an analysis plan and referring me to Greg Distiller, the statistician consultant on this project. To Greg thank you for your assistance and for speaking statistics in English!

To the Provincial Government of the Western Cape: Health Department officials: Dr Keith Cloete, for approval and support for the study as well as Dr Peter Bock and Meg Osler for sharing the Provincial ARV monthly statistics with me.

I would like to extend my heartfelt gratitude to Marilyn Smith and her team in the Knowledge Commons division of the UCT Library, who helped in rescuing my document, when my progress was hampered by technical difficulties. I especially

thank Nuroo Ismail and Diane Steele, who provided patient assistance, tender loving care and help during the final days. I am immensely grateful.

One person requires special acknowledgement for her role as friend, colleague and the only other member of my doctoral support group, Dr René Brandt. Thank you for your encouragement, 'handy hints', unselfish sharing of information and being the role model in demonstrating that we can achieve our goals within the timeframe set! I will always gratefully remember your encouragement and empathetic listening.

Finally, I wish to acknowledge my family and friends: My husband Lee Classen who has chosen to walk this path with me and has been a constant source of encouragement and practical support and without whom these past few years would have been much tougher. My son, Byron, who helped me from the beginning, with the database and fetching Mikhail from school when I couldn't and doing the household chores (even mine at times!). My youngest son Mikhail who was supportive, encouraging me to complete, imparting wise words and being willing to listen to my thesis, asking pertinent questions, being my co-editor and helping with the household chores. My sister Moira and her family, for all your love and support. I would like to thank Moira for reading the draft and providing useful comments, this was highly appreciated. My Mom and Dad for your love, encouragement and practical assistance. The many cups of tea and lunches especially during the last month of writing helped tremendously! My parents-in-law, Jenny and Lester Classen for your love and support (especially the home-cooked meals and 'dad's taxi!); Lastly, to my extended family and friends who are still my friends after the past three years of me being socially unavailable, even when we got together!

**I acknowledge all the caregivers of the children who participated in the study and were willing to give of their time and share their personal information, stories and feelings.**

**I salute you!**

# ABSTRACT

***Paediatric Antiretroviral HIV Treatment: Measurement and correlates of adherence in a resource-poor setting.***

**Objectives**

There is a paucity of data regarding paediatric adherence in resource-limited settings (RLS) especially among the very young age groups (<7yrs). The study investigated the rates of adherence, the identification of the adherence measurement, amongst four, which best correlates with viral load suppression; as well as correlates of adherence amongst a cohort of children younger than 7 years on antiretroviral HIV treatment.

**Design:** A Prospective cohort study with 6 months follow-up

**Methods**

Measures of adherence used: caregiver self-report (CSR), medicine measure/pill count, pharmacy refill and clinic attendance. Child, caregiver, socio-economic and health service characteristics were assessed for impact on adherence. Bivariate and multivariate analyses were used to determine agreement between measures and viral load outcome and to determine correlates of adherence.

**Results**

Mean age of children enrolled into the study was 27.08 months with a cohort mean adherence rate of 85% and mean viral load suppression of 74% at 6 months. Biological mothers were the majority primary caregivers (85%) and the majority (76%) of caregivers were unemployed with 60% receiving some form of social welfare grant. Results showed that caregiver self-reported adherence (CSR) was significantly correlated with viral load at 6 months (p=0.004). Correlations were found between clinic visits and pharmacy refill (highest values 0.35; p=0.000) and between medicine measure and clinic visits (highest value -0.21; p=0.04) but none of these measures were significantly correlated with viral load. Sensitivity and specificity analysis for CGSR showed that >95% adherence ensured a good viral load outcome. Four factors were significantly associated with adherence in bivariate analyses. These were: access to social welfare grants (OR=2.7; p=0.05); being counselled for initiation of ARV treatment by a counsellor vs. a doctor or nurse (OR 3.2, p=0.03); having another person in the household other than the index child infected with HIV (OR = 0.34, p=0.05) and caregiver depression (OR=0.07, p=0.01). However, in multivariate analyses certain other child, caregiver, socio-economic and health system characteristics as well as the above-mentioned variables emerged as significant.

**Conclusion**

Key findings indicate that adherence rates are relatively high in this cohort and CGSR is valid in a resource-poor setting but medicine measure was problematic as a paediatric HAART adherence measure. Certain child, caregiver, socio-economic and health system characteristics have a significant impact on adherence.

**Desireé Michaels**
**February 2008**

# PREFACE

The idea for this work had its origins during the period of intense 'ARV treatment activism' in South Africa. It became apparent that government needed to be convinced to adopt a national policy of providing ARV treatment in the public sector. In our eagerness to demonstrate the numbers in need of treatment, we focussed on the adults and children were left out of the specific targets and planning. Only those working directly with the children understood the barriers and challenges facing recipients of care and service providers in a context where all systems were geared towards adult treatment. In discussing my ideas with various people, it became apparent that there was a need to focus on access to treatment for children as well as adherence to treatment among young children since the common response became "no-one is investigating that in our setting!" In developing the protocol I became acutely aware of the lack of data regarding adherence to antiretroviral treatment among young children in resource-limited settings, especially the age group I finally chose (<7 yrs) and thus adherence became my area of focus.

I eagerly sent off my proposals for funding and received glowing reports of my protocol but with regrets that the study could not be funded. This continued until I decided that if I did not start somewhere, I would have had to wait till the world realized that this was an important area of investigation, by which time it might be too late for me to contribute to it. With the support of colleagues and mentors, I registered the protocol for a doctorate degree and began the research in 2004 when the National ARV 'roll-out' programme was in its infancy and less than 4000 children were on treatment in the entire country. In order to support my family and myself I had to continue employment in areas which were not always focussed on the present research. This was challenging since I had to do all the work related to this research, barring the interviewing.

In retrospect, the lack of funding was perhaps a blessing in disguise since it forced me to carry out operational research with no adaptations or extra resources into the system in which I was gathering data. I had no control of whether patients were transferred from the site before they had completed the study follow-up or when their

return appointment dates for follow-up were, neither was I notified when these were later changed. Their visit to the clinic took precedence and interviews were interrupted at times when their names were being called to see the doctor. I had no control over whether bloods were taken for viral load results or whether these results were recorded in the record keeping system once taken. The only resource I utilized was a private room to interview patients in a confidential manner. This was not easy to obtain because the IDC clinic does not have dedicated space like other outpatient clinics in the hospital and relies on various clinics to provide consultation rooms on the days when these were not occupied. Space, as in many clinics in South Africa was therefore a very scarce resource as well as a source of aggravation at times!

I am relating these constraints not to elicit 'sympathy' from the reader but to demonstrate that most challenges can be overcome with passion, co-operation and dedication. I have witnessed this same passion and dedication in others during the early antiretroviral programmes started in this country long before the government resources were provided. I can honestly say that my enthusiasm for contributing to this body of knowledge has not waned from commencement of the research to the completion of this dissertation.

It is gratifying to see that the world has realized that paediatric antiretroviral treatment and adherence is an important focus. In the last few years, there has been a global call to focus on the children and several advances have been made in addressing the issue of paediatric ARV treatment. I am therefore encouraged that the results of the present study is available at this time and that it provides direction for policy regarding health system intervention to monitor adherence and implement proactive strategies to promote adherence within the health service. The scope of this study can provide direction for the focus of future research into identifying barriers in resource-limited settings.

The high rate of adherence found amongst the study cohort is contrary to previous notions that those living in resource-limited settings would be unable to adhere to the strict demands of antiretroviral therapy. This notion has been refuted by adherence studies amongst adults in resource-limited settings and the present study adds to the body of evidence that paediatric populations in these settings are not different to their

adult counterparts regarding adherent behaviour. In my opinion, this attainment is an indication of the resilience of people living in poverty and overcoming challenges against all odds.

# GLOSSARY

| | |
|---|---|
| **AACTG** | Adult AIDS Clinical Trials Group |
| **AIDS** | Acquired Immunodeficiency Syndrome |
| **ART** | Antiretroviral Treatment |
| **ARV** | Antiretroviral(s) |
| **AZT** | Zidovudine |
| **CES-D** | Centre for Epidemiologic Studies Depression Scale |
| **CI** | Confidence Interval |
| **DDI** | Didanosine (type of antiretroviral drug) |
| **D4T** | Stavudine (type of antiretroviral drug) |
| **EFV** | Efavirenz (type of antiretroviral drug) |
| **EMD** | Electronic Monitoring Devices |
| **HIV** | Human Immunodeficiency Virus |
| **HAART** | Highly Active Antiretroviral Treatment |
| **IDC** | Infectious Diseases Clinic |
| **LPV** | Lopinavir (type of antiretroviral drug) |
| **MSF** | Medécins sans Frontiéres |
| **MOSSSS** | Medical Outcome Study Social Support Survey |
| **NVP** | Nevirapine (type of antiretroviral drug) |
| **NRTIs** | Nucleoside Reverse Transcriptase Inhibitors (class of antiretroviral drug) |
| **NNRTIs** | Non-nucleoside Reverse Transcriptase Inhibitors (class of antiretroviral drug) |
| **NSP** | National strategic Plan, which refers to the HIV & AIDS and STI Strategic Plan for South Africa 2007-2011 |
| **PACTG** | Paediatric AIDS Clinical Trials Group |
| **PCR** | Polymerase Chain Reaction (HIV–DNA test used to diagnose HIV in infants) |
| **PENTA** | Paediatric European Network for Treatment of AIDS |
| **PI** | Protease Inhibitors (class of antiretroviral drug) |
| **PMTCT** | Prevention of Mother-to-child-HIV transmission |
| **RTV** | Ritonavir (type of antiretroviral drug) |

| | |
|---|---|
| **STI** | Sexually Transmitted Infection |
| **TB** | Tuberculosis |
| **3TC** | Lamivudine (type of antiretroviral drug) |
| **UNICEF** | United Nation's Children's Fund |
| UCT | University of Cape Town |
| **WHO** | World Health Organization |

**Definition of children:**

All references to **children*** in this dissertation refer to those aged younger than 14 years - in line with the National definition used in relation to the ARV programme. This is due to the fact that pharmaceutically; children older than 14 years are treated using the adult treatment protocol in South Africa.

*It should be noted that this definition differs from the National (SA) definition of children, which refers to any person younger than 18 years.

**'Failure to take prescribed medicine for chronic diseases is a massive, world-wide problem. Patients fail to receive needed support.'**

Headlines of media release of WHO's publication of "Adherence to Long-term Therapies. Evidence for Action. 1 July, 2003. WHO, Geneva.

**"Significant progress has been made in treating HIV and AIDS since the virus was first identified 25 years ago, but along the way children have been overlooked. Children affected by HIV and AIDS have a right to equal access to treatment and care; without any significant increases in funding these rights will not be met."**

Global Movement for Children (26 May, 2006)

**"Opportunities for guiding exist in every small conversation. The way you speak with people, can improve adherence – you must help people find solutions within themselves. Adherence to life-saving medications is not going to be achieved by practitioners policing 'bad' behaviour. We are all aware of this."**

Stephen Rollnick, PATA conference (1st December 2005)

**"…despite an urgent need for paediatric treatment, alarmingly few drugs are available in formulations that are affordable and able to be administered to children while the development of new drugs continues to focus mainly on adults."**

Global Movement for Children (26 May 2006)

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES



# LIST OF GRAPHS

# CHAPTER 1
# SETTING THE HISTORICAL AND POLICY CONTEXT OF HIV AND ANTIRETROVIRAL THERAPY IN SA

## 1.1 Background

The HIV epidemic is into its third decade since it was first described as AIDS in the 1980s yet global HIV infection rates continue to increase. The WHO estimated that in 2006 approximately 39.5 million people in the world were living with HIV (1% adult prevalence) with 4.3 million new infections in 2006 and 2.9 million deaths due to AIDS (UNAIDS 2006). In 2007 this estimate was down to 33.2 million people infected with 2.1 million AIDS deaths. This reduction in estimate was attributed to more accurate data collection and analysis (Joint UN Programme on HIV/AIDS 2007).

Sub-Saharan Africa continues to bear the overwhelming burden of the disease with a 5.9% adult prevalence rate. Globally, HIV infection has increased particularly among adult women with 1 million more women over the age of 15 years infected in 2006 compared to 2004 (UNAIDS 2006). The 2007 UNAIDS report shows that 68% of the global number of people living with HIV, are in Sub-Saharan Africa and that eight countries in this region (including South Africa) accounted for approximately one-third of all new HIV infections and AIDS deaths globally (Joint UN Programme on HIV/AIDS 2007).

Great strides have been made in terms of our collective understanding of the causality and epidemiology of the disease, the structure and function of the virus as well as HIV treatment, especially since 2000 with the emergence of more antiretroviral treatment options for the adult population. It is estimated that global access to antiretroviral therapy (ARVs) has increased three-fold from 400 000 patients on treatment in 2003 to 1.3 million in 2005, with Highly Active Antiretroviral Treatment (HAART) (minimum of three ARVs) being the standard of care across the globe (Sharland et al. 2004); (Working Group on Antiretroviral Therapy and Medical Management of HIV

Infected Children. 2005). Sub-Saharan Africa has led this treatment scale-up as a result of resources and support from UNAIDS and WHO's 3 x 5 initiative[1], with the number of people receiving treatment globally during this period increasing from 100 000 in 2003 to 810 000 in 2005. It was estimated that approximately 350 000 premature deaths were averted in the developing world in 2005 as a directly result of the up-scaling of ARV treatment access (World Health Organization 2006a). According to UNAIDS/WHO, more than 1.6 million people living with HIV were receiving ARV therapy in low and middle income countries as of June 2006 (UNAIDS 2006).

Access to comprehensive HIV care and HAART for children in resource-rich settings has led to increased survival and improvement in quality of life. Despite evidence that HAART has improved the prognosis, growth and survival as well as quality of life of children in the 'developed world', research in paediatric HIV treatment in children younger than 15 years, living in resource-poor settings has not received the same priority and focus as that of research amongst the adult population (Verweel et al. 2002) , (Hutton & Oleske 2005), (Benjamin, Jr. et al. 2004; Brown, Lourie, & Pao 2000). This is even truer in respect of factors influencing paediatric adherence among children younger than 7 years. This may be due to the fact that the relatively small numbers of vertically infected children in resource-rich settings do not "warrant the investment" and that prevention strategies, namely, PMTCT have been largely effective.

Without any intervention, approximately one third of all children born to HIV-infected women will become infected themselves (World Health Organisation 2004). In the WHO 3 x 5 progress report (World Health Organization 2006b) it is noted with concern that access to prevention of mother-to-child transmission therapy remains unacceptably low in resource-limited settings with "fewer than 10% of HIV-positive pregnant women receiving antiretroviral prophylaxis before or during childbirth." The report further states that in 2005, 660 000 children under the age of 15 needed access

[1] WHO 3 x 5 strategy, launched in December 2003, was designed to encourage countries to achieve the goal of providing ARVs to 3 million people by 2005.

to antiretroviral treatment, representing 10% of the unmet global need and that nine out of ten children in need of treatment live in sub-Saharan Africa.

Clinical trials have shown that the PMTCT using dual therapy[2] can reduce transmission rates to 1.9% (Lallemant et al. 2004). In resource-poor settings this rate has been reduced to approximately 6% (Coetzee 2005). This implies that even with good PMTCT coverage and optimal reduction in vertical transmission rates between 2-6% of HIV infected pregnant women will transmit the virus to their children. Thus there will always be a need for ARV treatment for children, with adherence being a key component of treatment success.

## 1.2 The global burden of paediatric HIV infection

The estimates for the burden of HIV disease in children is less evident from epidemiological data due to the lack of specific reporting on children up till 2006 when UNICEF encouraged countries to provide child specific data[3]. A report released by UNAIDS on 26 November 2007 estimates the number of children infected globally at 2.5 million while the number of new infections among children was estimated at 420 000 in 2007. Ninety percent of these children live in resource-limited settings and are therefore without universal access to antiretroviral treatment. It further reports that new data indicated a levelling off of the global adult HIV prevalence and a decline in the number of new infections. However, South Africa has the dubious 'honour' of having the largest number of HIV infections amongst the adult population, in the world (Joint UN Programme on HIV/AIDS 2007).

Global mortality estimates amongst children under the age of 15 years, reflecting mostly vertically acquired infection, has declined from approximately 560 000 in 2001 to 380 000 in 2007 (Joint UN Programme on HIV/AIDS 2007). However, in sub-Saharan Africa, HIV/AIDS has become one of the leading causes of mortality in children under the age of five. A meta-analysis of nine perinatal trials conducted in

[2] This intervention involved using AZT given to the mother from 28 weeks in pregnancy. A dose of Nevirapine to the mother during labour and to the child within 72 hours of birth as well as a course of AZT to the child for 7 days after birth.

[3] All PEPFAR funded ARV programmes require a breakdown of ages of children on treatment etc. as part of their funding reporting criteria.

East, West Africa and South Africa revealed the stark contrast between mortality rates for infected and uninfected infants. Cumulative mortality rates for uninfected children at 12 and 24 months were 4.9% and 7.6% respectively compared with mortality rates among HIV-infected children of 35.2% and 52.6% respectively. An interesting observation from this analysis was that regardless of the child's HIV status, children whose mothers had died had a 3.5 times higher mortality risk. In-utero infection was a strong predictor of mortality and more than 50% of HIV-infected children died within the first two years of life. (Newell, M.-L., Coovadia, H., & Cortico-Borja, M. 2004)

In November 2004, WHO and UNICEF held a technical consultation on: "Improving Access to Appropriate Paediatric ARV Formulations" (UNICEF/WHO Technical Consultation 2004: 4). The meeting concluded that:

> "There are still very little reliable data on the number of children infected with HIV; progressing to serious clinical disease (and death) and reaching the immunological /clinical criteria for initiating ARV treatment. This lack of data hampers the ability of planning and procurement for HIV treatment and care programmes. In addition the insufficient articulation of burden of paediatric disease has also delayed both the political and technical response, as reflected in the absence of paediatric focus in national plans, targets and care strategies."

While the WHO developed a 3 x 5 strategy[4] to increase access to antiretroviral treatment in resource-limited settings, the main efforts in programme implementation appears to have benefited adults more than children. This view is borne out by the fact that all supporting programme infrastructures such as counselling and testing, monitoring, adherence support etc. have been aimed at adults. ARV scaling up efforts largely ignore the practical implementation of the roll-out for children such as appropriate drug supply and skilled paediatric health care workers, among other things (see Table 1.1), which limit access to treatment for children. A report compiled

[4] The progress report of 2006 acknowledges the failure of this programme in meeting its target of 3 million people on treatment in resource-limited settings by 2005. This initiative failed to treat even 50% of people in need of treatment according to The International Treatment Preparedness Coalition (ITPC, May 2006)

by the Global Movement for Children[5] concludes that only one in twenty HIV-infected children, who required treatment in resource-limited settings during 2004/5, received it. At present children receive mostly adult formulations such as tablets and capsules which need to be cut or 'opened' and diluted in water. There are few paediatric syrup formulations amongst the ARV regimens. Even when syrup formulations are available they are not readily used in resource-limited settings due to the prohibitive costs. Hence, many children are still dying needlessly despite the era of HAART.

**Table 1. 1: Minimum Requirements for Paediatric Friendly ARV programme scale-up**

| Factor | Requirements |
|---|---|
| Health care workers | • Doctors and nurses trained in paediatric HIV management and treatment.<br>• Paediatric ARV treatment literacy counselling skills |
| Health service resources | • Child-friendly scales and stadiometers to measure height and weight (for appropriate ARV dosing based on body surface area or weight band) especially for young infants.<br>• Access to laboratory facilities to do C4 cell counts, liver function tests and viral loads.<br>• Paediatric phlebotomy equipment.<br>• Paediatric nutritional intervention strategies and resources<br>• Pharmacy space to store large volumes of paediatric syrups (which take up more space than adult formulations (tablets and capsules) |
| ARV drugs | • Affordable<br>• Palatable for children<br>• Appropriate formulations (syrups vs. tablets) for infants and young children |

Data released by MSF at the XVI International AIDS Conference in Toronto in 2006, confirmed that children living in resource-poor settings have good outcomes on HAART but that the major obstacle to ARV roll-out in these settings, was the fact that paediatric formulations are "excessively overpriced, costing up to six times more than adult equivalents" (Médicins Sans Frontières 2006). They argued that the majority of children infected with HIV live in resource-limited settings hence the lack of interest in investment by pharmaceutical companies into the development of paediatric formulations.

[5] The group is comprised of the following organizations: Oxfam, Plan International, Save the Children, UNICEF, World Vision ENDA Tiers Monde and the Latin American and the Carribbean Network for Children.

## 1.3 The burden of HIV infection in South Africa

Statistics for the period during which the study was conducted, show that South Africa had amongst the highest ante-natal prevalence (30.2% of pregnant women attending public health facilities in 2005 and 29% in 2006) of HIV in the world. This generalized epidemic is however heterogeneous with the highest prevalence reported in KZN (39.1%) and the lowest in the Western Cape (15.7%) (Department of Health 2007).

Another study based on demographic modelling, suggested that women, aged 25-49 and female youth (aged 15-24) had the highest prevalence rates viz. 21.2% and 16.9 %, respectively compared to males 15.4% and 3.7%, respectively. It is estimated that there were approximately 527 000 new infections amongst adults by mid 2006 (Dorrington et al. 2006). The data suggest that women in South Africa (particularly those of childbearing age) are particularly vulnerable to HIV infection. This has implications for children born to women infected with HIV.

## 1.4 The burden of paediatric HIV infection in South Africa

Children under the age of 15 years comprise 32 % of South Africa's population (Statistics South Africa 2007). One estimate is that there are 2.2 million orphaned children in South Africa, half of whom have lost parents to AIDS (United Nation Children's Fund 2004). However, the true extent of HIV infection among children in South Africa is unknown. According to the results of the Human Sciences Research Council's (HSRC) survey (household survey using saliva HIV testing) approximately 7% of South Africa's children aged between two and nine years were infected with HIV in 2003 (Human Sciences Research Council 2004).

Demographic modelling using the annual national antenatal surveys among pregnant women attending antenatal clinics at public health facilities is probably our best source of data. It is commonly used to provide estimates of infection (Doyle & Millar 1990).

Dorrington et al (2006), using this method calculated that in one calendar year an estimated 38 000 babies were born with HIV infection, a further 26000 infected through breastfeeding and that approximately 235 000 children are among the estimated 5.5 million people living with HIV in South Africa in 2005. In the same study it was established that HIV prevalence rates in the Western Cape (the Province in which this study was conducted) rose to 15.7% among pregnant women (CI: 11.3-20.1) in 2005 during the period of this study which commenced in October 2004. The Western Cape Province has approximately 70 000 births per annum of whom approximately 10 000 births are born to HIV-infected women in the province. Despite the Prevention of Mother-to-Child HIV Transmission programme implemented in Khayelitsha (Cape Town) since January 1999 and in all other antenatal facilities in the public health sector in Western Cape by 2004, many children still become infected. With vertical transmission rates of between 5% to 10%, and good PMTCT coverage, we can still anticipate approximately 500 to 1000 infected children annually but more if there are gaps in PMTCT. The number of infected children in the province was estimated at 11 000 during the period 2005. This reflects cumulative survival (Dorrington R, 2006).

## 1.5 Child Mortality in South Africa: the role of HIV infection?

Maternal mortality data in general and child mortality data in particular, is relatively poor in South Africa with high levels of underreporting as well as a lack of a central reporting structure (Bradshaw et al. 2005). However, the WHO reports that South Africa is one of nine countries where under-five mortality is increasing with 66 deaths per 1000 live births estimated for 2003 with a projected 1.6 percentage increase per annum (Table 1.2).

**Table 1.2: Under-five mortality rates: estimates for 2003**

| | **Member State** | **Per 1000 live births** | **Uncertainty** | **Annual Average percentage change** | | |
|---|---|---|---|---|---|---|
| | | | | 1990-1994 | 1995 -1999 | 2000 - 2003 |
| 1 | Botswana | 112 | 96 - 128 | 2.6 | 8.9 | 3.5 |
| 2 | Cambodia | 140 | 124-158 | 0.9 | 2.4 | 1.2 |
| 3 | Côte d'Ivoire | 193 | 161-223 | 2.2 | 1.5 | 0.7 |
| 4 | Kenya | 123 | 108-138 | 2.7 | 1.6 | 0.8 |
| 5 | Kuwait | 12 | 11-13 | … | -4.0 | 2.1 |
| **6** | **South Africa** | **66** | **58-74** | **-0.3** | **1.3** | **1.6** |
| 7 | Swaziland | 153 | 140-166 | 0.0 | 5.2 | 2.5 |
| 8 | Turkmenistan | 102 | 93-112 | -1.7 | 2.2 | 1.0 |
| 9 | Zimbabwe | 126 | 111-141 | 2.4 | 5.4 | 2.5 |

**Source: World Health Organisation Excerpt from: Annex Table 2a**
http://www.who.int/whr/2005/annex/annexe2a_en.pdf accessed 12/11/2007

The Medical Research Council's report on the National burden of disease study in 2000 estimated the infant mortality rate to be 60 per 1000 live births while the under five-mortality was estimated at 95 per 1000 live births. Thus, approximately 60 000 children under five die in South Africa each year (Bradshaw, et.al. 2005). The three leading causes of child mortality are HIV/AIDS which account for 40% of <5 child deaths while low birth weight and diarrhoeal diseases together account for 30% (Nannan et al. 1998). If one recognises the association between maternal HIV infection and low birth weight (Dreyfuss et al. 2001); as well as the fact that diarrhoeal disease is one of the symptomatic features of HIV infection, then the contribution of HIV infection to the cause of mortality is increased substantially (Griffin 1990). Prevention of HIV infection and management of the disease particularly in women and children will therefore have the potential to have a major positive impact on child mortality in South Africa.

## 1.6 Prevention of HIV infection in children: PMTCT in South Africa

Approximately 75% of government clinics were providing PMTCT services by July 2007 and National Health's target was to have all clinics providing this service by December 2007 (PEPFAR 2007). However, HIV testing amongst antenatal clinic attendees in the country in 2005/6 was 45.2% with virtually no increase in numbers since 2004/5 (Barron et al. 2006).

In August 2006, WHO recommended that countries change the PMTCT regimen from monotherapy (single-dose NVP given to mother and baby at birth), to dual therapy for mothers with CD4 counts >200 cells/mm$^3$. Dual therapy involves giving the mother and child AZT and NVP. It further recommend HAART for pregnant women with a CD4 count of less than 350 cells/mm$^3$ or at stage three of the disease (World Health Organization 2006c). By in August 2007 South Africa had not yet adopted this protocol (The US President's Emergency Plan for AIDS Relief 2006 ). Appeals from clinicians and civil society in the HIV/AIDS sector, including the Treatment Action Campaign, to government led to the adoption of the new PMTCT guidelines by the Policy Committee of the National Health Council on Friday 25$^{th}$ January 2008 (Department of Health 2008). This will provide the impetus and resources for the dual-antiretroviral prophylaxis PMTCT intervention to be implemented across South Africa.

In contrast, the Western Cape Province has comprehensive coverage and implementation of the PMTCT programme. By May 2003 approximately all antenatal (300 sites) and child health clinics including mobile services offered the programme. Since 2002, dual therapy (AZT and Nevirapine) was implemented as a pilot project with full implementation since 2003. Dual therapy is given to both mothers and children with the exception of women with a CD4 count of less than 200 who are offered triple therapy during pregnancy with a view to continuing therapy after delivery. Children were tested for HIV infection at 14 weeks[6] of age using the HIV DNA Polymerase Chain Reaction test (PCR). A study conducted in Khayelitsha in 2004 reported a 6% transmission rate using this regimen (Coetzee et al. 2005)

[6] This policy was subsequently revised in 2007 and testing of infants since then is at 6 weeks of age.

On the other extreme in Kwa Zulu Natal (KZN) it is reported that even at sites where PMTCT[7] is delivered only between 49-80 percent of women at ante-natal clinics accept voluntary counselling and testing. Among those who are tested positive only between 10-60% get the intervention and less than half of their babies get tested after birth. The transmission rate is estimated at 20.8% in this province (Rollins et al. 2007). It is expected that once the new PMTCT national policy is implemented, it will impact positively on vertical transmission rates. The current high transmission rates in some parts of the country imply that there will be a vast pool of HIV infected children, who were born during these past years during which women had limited access to effective PMTCT interventions, who will require ARV treatment in future if they survive their first few years of life.

Data on vertical transmission rates were not gathered routinely in South Africa at the time of writing. Despite PMTCT coverage in approximately 80% of public health facilities, indications are that the national PMTCT programme is not currently successful as the 2006 antenatal clinic survey found that 29 percent of attendees (168 000 women) were HIV infected but only 44% of them had received the ARVs to prevent vertical transmission (Department of Health 2007b).

## 1.7 Access to Antiretroviral Treatment in South Africa

### 1.7.1 Historical overview of HIV and AIDS Policy

The development of strategic policy documents to address the HIV epidemic in South Africa has a fifteen-year history. A brief overview of this history illustrates the progress that has been made (though it may be argued that we have not gone far enough with what we had at our disposal).

In 1992, the National AIDS Co-ordinating Committee of South Africa (NACOSA) was launched with a mandate by former President Nelson Mandela to develop a national strategy on HIV and AIDS. Cabinet endorsed this strategy in 1994 (this was

[7] The national policy of providing monotherapy was implemented in KZN at the time of writing.

against the background of the demise of Apartheid and the rising epidemic among the heterosexual population identified in the 1980s.) HIV infection was first thought to be prevalent only among gay men in South Africa). In 1990, the first national antenatal survey was conducted. This became an annual form of surveillance providing the statistics on the trajectory of the South African epidemic and the basis for modelling studies in later years.

In 1997, a review of the National AIDS Co-ordinating Committee of South Africa (NACOSA) made the need for a multi-sectoral approach to the epidemic apparent. This led to the development of the National Strategic framework for HIV, AIDS and STIs (National AIDS Plan) initiated by the Minister of Health, Dr Manto Tsabalala-Msimang in July 1999 in response to President Thabo Mbeki's challenge to all sectors of society "*to become actively involved in initiatives designed to address the HIV/AIDS epidemic"* (Department of Health 2000: 5). At that stage, in 1999 the HIV prevalence among pregnant women in the country was 22.4%.

The 2000-2005 Strategic Framework for HIV, AIDS and STIs included fourteen instances in which children were referred to. However, the main thrust of attention to children was in the context of "AIDS orphanhood" and one objective related to the development and implementation of "programmes to support health and social needs of children affected by HIV/AIDS" including the facilitation of adoption of AIDS orphans (p.25). In not addressing HIV-infected children, the intention of the document was clearly not to improve access through identification, care and treatment of HIV-infected children, since this document was written in the pre-ARV era.

The period between 2000 and 2005 was a very volatile period in relation to government's response to the epidemic, international and civil society's expectations and the HIV epidemic trajectory in the country.

In 2002, the High Court ordered the government (in the light of its refusal to implement the PMTCT programme nationally) to make Nevirapine available to pregnant women to help prevent mother to child transmission of HIV.

In 2003, government approved a plan to make antiretroviral treatment publicly available and this programme has been rolled out since April 2004. The launch of the National ARV-rollout necessitated yet another policy document on AIDS which superseded the 2000-2005 Plan and the "Operational Plan for comprehensive HIV and AIDS Care, Management and Treatment for South Africa" (Operational Plan), was launched in November 2003. The goal of the 2003 Operational plan was for at least one service delivery point in each district to be able to provide ARV treatment at first, followed by continued rollout of services.

In preparation for the ARV rollout, the government drafted guidelines to assist service providers in the management of patients on ART. The guidelines, based on those formulated by WHO, provide a detailed description of administration of ART in adults and children, management of adverse events in these two groups, and adherence to therapy, including the management of post-exposure prophylaxis. The goals of the ARV programme: how patients are to be selected for ARVs, and what regimens are to be administered are detailed in the document. Tuberculosis (TB), which commonly co-exists in patients infected with HIV, is also discussed. The national ARV treatment guidelines serve as the minimum standards to be followed by service providers. However, this plan was deficient in the attention given to children and adolescents in key areas such as early identification and entry into care and human resource skills and competencies specific to paediatrics (Michaels et al. 2006a). Further details of this critique are elaborated below.



### 1.7.2 Critique of South African National Operational Plan (2003)

A review of the deficiencies of this initial ARV roll-out plan in respect of paediatrics is necessary to provide a policy context for the service provision in respect of children infected with HIV during the period of the reported study.

#### 1.7.2.1 Access points to ARV treatment

The operational plan outlined several "entry points" for ARV treatment. It noted that strategies for infant HIV testing were coordinated by the PMTCT program and

recommended that "a paediatric monitoring task force be established, and charged with coordinating protocols for infant diagnostics and monitoring with the PMTCT program and the NHLS" (p.170). However, the plan was silent on strategies for strengthening and expanding the testing of HIV-exposed and the identification of HIV-infected children beyond the PMTCT programme.

The issue of disclosure of the child's HIV status to the child is unique to the management of children. There is never an instance where an adult's HIV status is kept a secret from him or her (except, possibly in the case of mentally challenged individuals), but in practice this is very common in the management of paediatric patients. The plan did not refer specifically to any special considerations regarding the counselling needs consequent on testing children of varying ages nor about the counselling needs of caregivers.



#### 1.7.2.2 Antiretroviral Therapy in Paediatrics

Several issues regarding ART in children were covered in the plan, including the following: (1) confirmation of HIV-positive diagnosis, (2) guidelines regarding initiation of treatment, (3) national paediatric drug regimen protocol, (4) the use of cotrimoxazole for prophylaxis of opportunistic infections and (5) Nevirapine resistance monitoring. However, in the ensuing discussion on "changing or stopping antiretroviral treatment," adverse event reporting, patient-drug readiness training, adherence, and adherence strategies, no reference was made to children or to the specific circumstances regarding children on treatment (e.g., caregiver issues). The issue of paediatric treatment was notably absent in the section entitled "special considerations" (p. 40), which included guidelines for the South African Military Health Service and Correctional Services.

A discussion paper on the paediatric ARV rollout in South Africa examined the 2004-2006 national plan (Shungking & Zampoli 2005) and concluded that children's issues were not addressed comprehensively but instead restricted to clinical and technical issues. For example, family care or comprehensive considerations of the mother-infant pair was not promoted adequately. The plan did not make special provision for

children who did not have an identifiable caregiver and the special needs and vulnerabilities of infants, school-going children, and adolescents were not considered.

However, a separate document that predates the operational plan, "Policy guidelines for youth and adolescent Health"(Department of Health 2001) addressed some of the needs of HIV-infected adolescents. This document contained comprehensive policy guidelines for South African youth and adolescents aged 10 to 24 years, and acknowledged that adolescents and youth living with HIV/AIDS constituted a vulnerable group. It stated that the lives and well-being of infected youth could be improved if (1) their living environment was non-discriminatory, (2) they had adequate shelter and nutrition, (3) they had access to treatment for opportunistic infections, and (4) they were supported. A major weakness of this and subsequent plans, is the lack of attention to the specific needs of the very young child (<2 years) including the monitoring of ARV provisioning to this age group.

The Operational Plan made provision for nutrition-related interventions, consisting of vitamin syrup and a supplement meal, for HIV-infected children under 14 years (p.42) (Department of Health 2003). It is under the heading of 'nutrition' that the issues of caregivers and child-headed households as well as the need for "appropriate" counselling are referred to for the first time. However, this reference to counselling only alluded to nutritional management and neither antiretroviral treatment literacy nor medicine administration strategies were mentioned.



#### 1.7.2.3 Continuum of Care Services

The nature of childhood conditions and diseases lends itself to frequent up-and-down referral between various health service levels and services. It may therefore be even more critical in the case of paediatric HIV care and treatment, to have a care coordinator. However, the plan did not elaborate on how to implement the principle of a designated patient care coordinator, especially with regard to paediatric patients.

### 1.7.2.4 Accreditation of Service Points[8]

There were no explicit accreditation criteria for paediatric ARV treatment service points in the plan, instead it was assumed that the criteria were generic and did not exclude paediatric sites (Department of Health 2003). However, in the case of paediatrics, the criteria requiring availability of a trained care team on-site with representation of all relevant professions (clinicians, nurses and counsellors) may be difficult to achieve since not all clinicians are proficient in paediatric HIV management. In addition, most service points familiar with the care of young children, particularly primary care clinics (EPI, IMCI) are nurse-driven services. The lack of skilled paediatric trained personnel has been a major barrier to delivering ARV treatment for children less than six years of age (Michaels 2006b).

### 1.7.2.5 Planning for and Monitoring the Paediatric ARV Rollout

There was insufficient attention to child-specific aspects of monitoring and evaluation of the ARV program and subsequently, fewer resources allocated to facilitate access to treatment for children less than 14 years of age. The lack of stratification of child age groups has led to a lack of monitoring of the numbers of very young children on ARVs in South Africa. Although it was explicitly stated in WHO's 3 x 5 global target that approximately 10 to 15 percent of the total number of people on treatment should be children (World Health Organization 2003a), the projected number of patients on treatment in South Africa's Operational Plan did not distinguish between children and adults. The operationalization of the monitoring process for the ARV roll-out was deficient regarding information about the number of children on treatment since the report form only required the number of paediatric ARVs to be reported.

It should be noted that this issue was brought to the attention of the National Health Authorities by the author and colleagues during a rapid situational analysis of the

[8] The National Health Department accredited 122 sites by March 2005 of which 113 were operational. This process took longer than anticipated and the function of accreditation was subsequently devolved to the Provinces by 2005 (Stewart R & Loveday, M.(2005).

paediatric ARV roll-out in South Africa at a meeting held 22 September 2005 (Michaels 2005). The added voice of the Joint Civil Society Monitoring Forum led to the revision of the departments reporting system for the ARV roll-out and since the end of 2005, the report required that the total number of children under 14 years be reported separately (Osler, M. 2007. Personal communication, 9 August).

### 1.7.3 The Plan Beyond 2006

The revised HIV/AIDS and STI National Strategic Plan (NSP)(Department of Health 2007a) launched in April 2007, describes terms for a national roll-out of ARV treatment and is estimated to cost approximately R25 billion. The Plan was finally hailed as "bold" and "one of the best responses to the epidemic in terms of a national framework" which aims to decrease new HIV infections by 50% and brings treatment support to at least 80% of HIV-infected people by 2011. It recognizes that young people in the age group 15-24 should be the focus of all interventions, especially behaviour change based prevention (News 24 2007). The lack of specific targets and allocation of responsibilities in the previous plan is acknowledged and rectified in the 2007-2011 NSP. The document outlines guiding principles, which includes the following child-specific reference:

> "**Protecting and Respecting Children**: The impact of HIV on the ***rights of children*** is enormous. Respect for the best interests of the child dictates that children's rights and needs must be at the forefront of all interventions for HIV prevention, treatment and support" (Department of Health 2007a:56).

South Africa is a signatory to two major treaties which afford protection of children's rights, namely,: the United Nations Convention on the Rights of the Child (Secretary-General of the United Nations. 1989) and the African Charter on the Rights and Welfare of the Child (ACRWC) (Secretary General of the Organisation of the African Union 1990). In addition, the South African Constitution, Act 108 of 1996 outlines the States' obligation in protecting the rights of the child. The clear intent to protect the rights of children, including the right to life and basic health care services, is evident in the commitment to the principles enshrined in the above-mentioned documents. However, the challenge remains in the realisation of these rights. With

regard to HIV and AIDS the issue of children's access to testing, care and treatment remains a policy as well as an implementation challenge in South Africa.

During 2005, child activist groups and concerned paediatricians in South Africa, signalled the need to factor children into the targets for ARV treatment access in a more systematic and specific manner (Children's Rights Centre 2005; Department of Health 2005).

South Africa is a member of the African Union and a signatory to the United Nations General Assembly Special Session (UNGASS) Declaration. In May 2006, the African Union agreed that by December 2006 its countries would include "revised, quantified national targets for prevention, PMTCT, AIDS treatment and care and support that are consistent with, and contribute to, the Africa wide targets (African Union 1990: 7). While the South African health system strains under the additional load created by HIV infection, there is a concerted effort to give attention to children's access to HIV management and treatment as demonstrated in the 2007-2011 National Strategic Plan on HIV and AIDS.

Nineteen goals are specified. Each goal specifies several specific objectives together with five-year targets and assignment of roles amongst lead agencies responsible for the achievement of these targets. Nine of the nineteen (47%) goals incorporate objectives and interventions which mention or affect children directly. These range from legislation, social security, education, mental health, developmental monitoring to HIV prevention and HIV management and treatment. The plan has many ambitious goals and implementation strategies, some of which require policy and legislative changes (Michaels & Eley 2007).

## 1.8 ARV Roll-out Progress in South Africa (2003 -2006)

South Africa has one of the largest antiretroviral treatment programmes in the world. There is no doubt that the need for treatment remains far greater than what is available. UNAIDS estimated that approximately 800 000 people in South Africa urgently needed treatment in 2005/6 and the majority did not receive it (International

Treatment Preparedness Coalition 2006). In November 2006, the Department of Health issued a press release stating "The accumulative number of both children and adult patients put on antiretroviral therapy by September 2006 was 213 828" (Department of Health 2006) of whom 21 550 were children younger than 14 years; clearly below the UNAIDS estimate of those in need of treatment. By December 2006, South Africa only achieved 36% of the National ARV roll-out targets set in 2003 for the number of persons on treatment (Joint Civil Society Monitoring Forum and Department of Health 2007).

According to the WHO 3 x 5 strategies for increasing access to treatment (World Health Organisation 2003a), 10% of those on treatment should comprise of children younger than 14 years. In this regard, South Africa has met the target. However, this apparent achievement belies the fact that most of the children on treatment are found at a few urban hospitals (International Treatment Preparedness Coalition 2006).

### 1.8.1 The Western Cape ARV Programme

#### 1.8.1.1 Historical Background to ARV Roll-out

The Western Cape experience deserves special mention since this was the location for the study and it was the first Province to have Provincial government support for the implementation of both PMTCT and ARV programmes at public health facilities. It provided the necessary data and experience for the decision by government to implement the National ARV roll-out programme.

The HAART programme was initiated as a "pilot project" at three clinics in Khayelitsha (Western Cape Province) in 2001, both ahead of the National ARV roll-out and amidst strong National government opposition. During the years between 2001 and the end of 2003, this programme was financed and managed by Medécins Sans Frontiéres (MSF). The HAART programme in Khayelitsha was adult focussed though children were also initiated on HAART at these sites, during this period.

In the Western Cape, approximately 700 children were on HAART by March 2004, with approximately two thirds of these children treated at the three tertiary hospitals (Red Cross Hospital, Groote Schuur Hospital and Tygerberg Hospital). Treatment was predominantly research and donor funded at this time. The majority of these children were under the age of 6 years and thus dependent on caregivers for their access to health care and adherence to treatment. By the end of the study period (October 2006) the number of children on treatment in the Western Cape had risen to 2611 (Bock.P. 2006 ).

The Western Cape Provincial Health Department works closely with clinicians and academics to ensure that protocols and policies are adapted to address the needs and meet the targets for the antiretroviral treatment programme. A strategic decision was made to encourage the tertiary hospitals to transfer stable paediatric patients on HAART out to the primary care clinics and then have paediatricians mentor and train clinic staff to manage and treat infected children. This strategy was implemented since the end of 2005.

## 1.9 Key Barriers to Paediatric Access to Treatment in South Africa.

Access to ARVs hinges on disease staging using laboratory and clinical indicators. The current practice of taking blood from veins for CD4 counts and viral load testing poses a particular challenge in young children and infants because of the lack of skilled personnel willing and trained to do this task. Phlebotomy skills will enable early identification of infected children for entry into care. HIV care that can improve the quality of life for children infected with HIV includes cotrimoxazole prophylaxis, growth monitoring, nutritional interventions, and treatment of opportunistic infections. This in turn calls for a level of clinical expertise relevant to paediatrics.

Major challenges to the paediatric rollout as perceived by health care workers surveyed in South Africa, included clinic space constraints, lack of adequately trained staff, lack of clinical capacity and a "fear of treating children" (Michaels 2006a). In particular, the need for nurses to be skilled in taking blood from children was cited. Doctors and nurses also noted gaps in the health system, particularly between the

PMTCT program and well baby (immunization) clinics. Concerns raised by respondents included fewer drug options for children and lack of services for adolescents. Widespread poverty and unemployment and the impact of these factors on access to health care; transport and distance were reported as barriers to accessing paediatric HIV care due to limited paediatric ARV sites. The lack of community awareness about ARV services for children and the benefits of such services for infected children was another concern raised. Counsellors and pharmacists expressed other concerns surrounding community awareness and support for children with HIV as well as mentioning issues regarding medications including dosing, maintaining stock levels and monitoring of adherence. Many health care workers cited the emotional challenge of working in the currently constrained system.

Thus, several child-specific challenges beset the South African pubic sector health care system, with inadequate paediatric formulations being among these. The lack of appropriate paediatric ARV formulations is not unique to South Africa and global lobbying for the development of paediatric ARV's is occurring through groups such as MSF (SA), Treatment Action Campaign and the Global Movement for Children (Global Movement for Children 2006). Lack of adequately trained human resources to deal with paediatric HIV care and treatment is one of the primary barriers to access in South Africa.



## 1.10 Conclusion

There is a paucity of data relating to paediatric HIV infection, management and treatment on a global scale. Sub-Saharan Africa bears the greatest burden of HIV in the world and children are not specifically targeted for intervention due to a lack of child-specific monitoring and allocation of resources. Paediatric HIV infection has become a rare event in most resource-rich settings due to the effective implementation of PMTCT programmes. This however is not the case in resource-limited settings where the provision of services and access to PMTCT programmes are more challenging. Lack of early identification of HIV-infected children together with a lack of skilled human resources to manage paediatric HIV infection effectively, has led to an increased burden of paediatric HIV infection particularly in South Africa.

From a public health perspective, those who have access to antiretroviral treatment and those who decide who gets access, have an obligation to preserve the integrity of the limited number of ARV's available (i.e. preventing resistance as far as possible). One way in which this can be done is by ensuring near perfect adherence to treatment, a very challenging prospect considering that ARV treatment is life-long and in the case of a child who is vertically infected, this includes various stages of growth and development.

In Africa, the AIDS pandemic has taken its toll on families, resulting in many children being orphaned and left in the care of multiple caregivers or living in child-headed households (United Nation Children's Fund 2004). These unique aspects; adherence by proxy (via a caregiver) and multiple caregivers, make paediatric adherence to HIV treatment very challenging.

In summary, chapter 1 explored the epidemiology of HIV infection, firstly on a global scale and then in South Africa, with particular emphasis on the statistics during the period of the study, namely, 2004-2006.[9] An overview of child related mortality in SA highlighted the impact of HIV infection on children. The progress of the PMTCT programme in SA (the main prevention strategy affecting children) was provided in a manner which contrasts two of the Provinces in the country, demonstrating the heterogeneity of the epidemic. A brief historical overview of the development of the HIV strategic policies in SA gives the reader background to the development of the SA National Operational Plan (2003-2006) governing the period of the study. A detailed critique of the Plan was presented in respect of child-specific issues as well as commentary on the HIV/ AIDS and STI National Strategic Plan 2007-2011 before concluding with the key barriers to paediatric access to treatment in SA.



[9] Statistics were presented to cover the period of the study, namely, 2004 – 2006. Where applicable statistics for 2007 was presented.

## 1.11 Study Rationale

The rationale for this study is supported by the fact that the burden of paediatric HIV is and will remain large for South Africa and many developing countries and therefore there is a need to address and improve paediatric adherence to treatment. Whereas there was some literature on adherence among adults, including South Africans, there was very little on children generally and practically nothing on young children, particularly in South Africa[10] (Stone et al. 2004; Chesney 2003; Orrell et al. 2003; Coetzee et al. 2004; Durvasula et al. 2002).

The consequences of poor adherence to antiretroviral treatment in children are the same as that of no access to treatment, namely, increased morbidity and mortality. In addition, resultant viral resistance cannot easily be addressed since there are limited options for treatment in general and for children, in particular. Antiretroviral treatment is for life and this 'time frame' will be longer in children than in adults and thus the need for longer maintenance on first line treatment is essential in paediatrics. These reasons demand that paediatric adherence be studied and that the 'best' measures and predictors of adherence are understood in order to facilitate optimal adherence.

Information from studies amongst adults cannot be generalized to the paediatric population. Paediatric HIV and treatment is different to that of adults. There are clinical as well as social differences. Firstly, the majority of children younger than seven years have contracted the disease through vertical transmission while their immune systems have not had an opportunity to mature. HIV disease progression in infants and young children is therefore compressed into a relatively short space of time compared to adults for whom the time from infection to AIDS is considered approximately ten years. Secondly, the long-term effects of HAART in children are largely unknown due to the limited research in this area compared to clinical trials involving adults. Finally, young children are dependent on caregivers for access to health care as well as adherence to medication and treatment. These reasons, amongst

[10] At the time of protocol development, there were no studies on adherence among children younger than 7 yrs in South Africa. Subsequently, two studies were published in 2007(one in Cape Town and one in KZN).

others, necessitate the investigation of paediatric adherence to HAART in general and in resource-poor settings in particular.

This study is important in the context of paediatric HIV management in Sub-Saharan Africa. The gains in lower drug prices for ARVs have influenced access to antiretroviral treatment for more people in Southern Africa. This has potentially increased access to HAART among the general population and in a limited way to children. The drug prices for paediatric formulations still remain prohibitive, for example, Zidovudine syrup could cost up to 5 times more than the adult formulation (Médecins Sans Frontières 2006). However, with increased international lobbying and pressure from United Nation's Children's Fund (UNICEF), it is envisaged that access to treatment among children will increase, especially in Sub-Saharan Africa which bears the brunt of the AIDS epidemic.

It is widely acknowledged that prevention of mother to child transmission is the ideal way of "managing" the epidemic among children. However, there is a legacy of infected children born prior to the PMTCT intervention being available in many parts of Southern Africa including South Africa, who have survived. In addition, there are children born to HIV infected women who live in areas where there is coverage of PMTCT, but for various reasons, these women do not access, due to 'overstretched' health systems or lack of 'uptake' and finally there are children born to HIV infected women who are infected despite their mother's participation in PMTCT programmes. Thus, paediatric HIV infection will remain a challenge to Sub-Saharan Africa in general and South Africa in particular for a long time.

Few studies on HAART adherence have focused exclusively on children between the ages of birth to seven years, as is illustrated in Chapter 2. This study is therefore timely because it commenced during the implementation of the National roll-out of antiretroviral treatment in South Africa. It focuses on two key issues regarding paediatric antiretroviral treatment in resource-poor settings, namely, identifying methods for measuring adherence and factors influencing adherence among children younger than 7 years of age in order to inform the development of appropriate interventions to increase and maintain paediatric adherence to treatment.

# CHAPTER 2
# LITERATURE REVIEW

## 2.1 Introduction

This chapter provides an overview of the contextual issues regarding paediatric adherence to HAART and reviews the literature against which the study is framed.

Firstly, terminology and definitions of adherence are outlined. Secondly, an overview of the various methods of adherence measurement and concepts of thresholds of adherence are presented. Thirdly, factors influencing adherence among children, are reviewed. These factors are conceptualized within four sub-domains, namely, child, caregiver, Socio-economic and health system factors. Finally, a brief overview of adherence enhancing tools is provided.

The review draws mainly on paediatric studies with the aim of focussing exclusively on children younger than 7 years of age. However, there was a paucity of specific data for this age group. Most paediatric adherence studies involved wide age ranges. It should be noted issues related to adolescents and young adults infected with HIV, is beyond the scope of this review and research cited which includes this age group, is incidental to the focus on children. All references to children in this and subsequent chapters, refer to those aged younger than 14 years. The choice of this definition to define the parameters of the present study is motivated by the fact that pharmaceutically; children older than 14 years are treated using the adult treatment regimen in South Africa. However, studies included in the review have wide age ranges (up to 21 yrs, at times) and do not necessarily adhere to the same definition.

Further, because adult caregivers play a central role in the adherence of children, the review was extended to studies among HIV infected adult populations in consideration of caregiver characteristics which may influence adherence. The review is not grouped according to adult vs. children specific reviews but rather according to

issues and where relevant evidence is available from adult studies, these are cited and acknowledged.

A gap identified in the review is the lack of sufficient data on paediatric populations in resource-limited settings. As noted below in the review methodology section, only thirteen paediatric adherence studies were identified from resource-limited settings. Thus, in exploring what is known about paediatric adherence, material is drawn from both developed and resource-limited settings.

## 2.2 Review Methodology

An electronic search of English language published literature and conference proceedings on paediatric adherence from 1998 to July 2007 was conducted. The search strategy involved searching the following databases: PubMed, ISI Web of Science, Psych Info, Ebsco Electronic Journals Services and Silverplatter, Science Direct. In addition, manual searching of references from retrieved articles provided additional sources of information. Abstracts of the following AIDS Conference proceedings were searched: 12th World AIDS Conference, Geneva, 1998; International AIDS Conference (2002 and 2007) ; 2nd International Conference on HIV Treatment Adherence, 2007; 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, 2005; 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, 2007; 2nd International IAPAC Conference on Adherence, 2007 and the Paediatric AIDS Clinical Trial Group Meeting Proceedings, 1998 and 1999.

The following combinations of search terms were used: "HAART adherence Children"; "HIV and children"; "paediatric adherence"; "p(a)ediatric ART"; "adherence children"; "HIV compliance"; "factors HAART adherence"; "HIV and caregiver"; "adherence and measurement"; "adherence measure"; "pharmacy refill and HIV"; "caregiver and self-report"; "clinical outcomes and HIV children"; "pharmacokinetics and HIV"; "P(a)ediatric intervention and HIV"; "disclosure and HIV"; "social grants" and "adherence"; "adherence" and "resource-limited settings" ; "factors" and "adherence" ; "tools" and "adherence" ; etc.

Only 13 relevant paediatric adherence studies (Table 2.4) were located including studies located in: Africa (9), India (2) and Asia (2) among paediatric populations but excluding studies conducted exclusively among adolescents. This paucity of data led to the author reserving critical appraisal by not excluding studies on the basis of quality though several included adherence measurement as incidental to clinical trial outcomes and not as the main focus of the study; or, adherence studies had small sample sizes with wide age ranges.

## 2.3 Terminology

The terms 'compliance' and 'adherence' both refer to the patient's ability to follow a treatment plan. However, in the literature, the term 'adherence' has gained popularity in the context of HAART due to the fact that the term compliance connotes controlling, unequal power relations. In contrast, 'adherence' implies collaboration between patient and provider and extends beyond medication management, to encompass a comprehensive treatment plan. The term "adherence" is used in this dissertation to reflect this broader concept.

## 2.4 Definition of Adherence

The concept of adherence to medical treatment appears to be a complex one in general but more so with regard to paediatric adherence. The various definitions postulated from different perspectives are explored.

The classic definition of adherence is "the extent to which a patient's health-related behaviours correspond with medical advice" (Eldred 1997).This definition therefore leads to the conclusion that non-adherence applies to both the overdosing and the under dosing of medication (Urquhart 1992).

Another, more HIV-specific definition has been postulated:

> "the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination

> medication regimen to control viral (HIV) replication and improve immune function"p.186 (Simoni, et al. 2003) .

This definition is limited to treatment as drugs while the definition below is much more inclusive of all treatment-related 'behaviours'.

A conceptual definition for paediatric adherence postulated by De Civita & Dobkin (2004) indicates that paediatric adherence involves a triadic partnership involving the medical team, caregiver and child. They define paediatric adherence as:

> "… the manifestation of multiple treatment-related behaviours prescribed by a medical team, which is influenced by development and contextual characteristics, shaped by disease, and interpreted by the caregiver and individual child."(De Civita & Dobkin 2004: 158)

This is a more operational definition of adherence and one that guides us to study factors that influence the "manifestation of multiple treatment-related behaviours" in order to promote full adherence to treatment.

Clearly, when one talks about a patient being "adherent", the implication is that they're taking 100% of their medication, 100% of the time and are consequently likely to have undetectable viral loads (in the case of treatment naïve patients commencing HAART). Anything less would be understood as 'non-adherent.' Previous adherence experience with other chronic medications has led us to believe that this goal of 100% adherence to HAART is both unattainable and unrealistic. For example, average adherence rates for antihypertensive medications were found to be 50% in a study by (Sackett, et al. 1975)) and even for medical regimens to which adolescents would be motivated to comply, such as acne medication, data showed a 49% adherence rate (Flanders 1984).

The quest for consensus around a definition of adherence is not unique to HAART. Definitions of adherence for well-established disease management programmes such as Tuberculosis control have no agreed definition of adherence either. However, it is well accepted that "TB compliance" is defined as; at least two thirds of treatment

taken during at least one of the two phases of TB treatment. Some studies have put this 'compliance' rate between 70-80% (Urquhart 1992).

Defining adherence success is complex because of the lack of specific measures and tests for HAART adherence.

## 2.5 Measuring Adherence

There is no 'gold standard' for measuring adherence to HAART but several methods have been employed. Adherence measurement tools for HAART fall broadly into three categories, namely, (1) subjective measures of adherence based on self-report or others' report of adherence (e.g. clinician), including medical chart review. (2) Objective measures of adherence such as pill counts, pharmacy refill records, clinic attendance records, use of mechanical or electronic pill monitors that document when medication bottles are opened (e.g. MEMScaps) and (3) Physiological methods or indicators such as plasma drug level testing, undetectable viral load results and increased CD4 count. The latter mentioned measures are used to indicate treatment response rather than measuring adherence per se. Some studies use multiple methods of monitoring but by far the most popular methods are subjective measures of adherence assessment.

Most information regarding these methods is obtained from studies conducted amongst adults. These methods have limitations particularly when applied to paediatric adherence monitoring. For example, 'pill counts' are complicated when paediatric syrups are used. Children often have multiple caregivers and the primary caregiver may prepare medicine doses ahead of time for the other caregiver to administer at a later stage, thereby negating the findings of electronic measuring devices such as Medication Events Monitoring Systems (MEMScaps). Furthermore, syrups are often spat out or vomited and thus doses repeated, leading to the often erroneous conclusions of over 100% adherence in medicine measure. Caregivers' reports' may differ from the child's and a study in the USA found kappa statistics for agreement between adults and their children for adherence variables ranging from 0.05 to 0.32 which indicate poor to extremely poor agreement (Dolezal et al. 2003).

### 2.5.1. Self-report adherence questionnaires

Patient self-report is the most common measure used in studies of adherence to antiretroviral treatment. For example, in their review of adult focused adherence literature, Fogarty et.al. found 50 of 57 abstracts and 15 of 18 articles used subjective methods in their studies on adherence (Fogarty et al. 2002). Likewise, a meta-analysis of studies to determine estimates of adherence among adults in North America and Sub-Saharan African populations, found 71% of 31 studies in North America and 66% of 27 studies in Africa, used self-report as a measure of adherence (Mills 2006). A review of paediatric adherence studies found 13 of the 32 studies reviewed used caregiver self-report as the measure of adherence (Simoni,J. et al. 2007).

There are several variations of the self-report questionnaire (Table 2.1). Self-report adherence questionnaires tend to adopt two main approaches, namely, (1) to identify attitudes or obstacles to adherence (Morisky, Green, & Levine 1986) , (Frick et al. 1998), (Pekovic et al. 1998) and (2) a more direct approach to determine adherence (dosing questions) on specific days before a clinic visit (Bangsberg DR, Hecht, & Charlebois 2000) ;(Chesney 2000a) ;(Fletcher, Pappius, & Harper 1979).

Self-report questionnaires vary with respect to the time frame covered from between 2-day to 7-day recall prior to clinic visit, with 3-day self-report being the most popular method based on the premise that it reduces the probability of recall bias. No empirical studies have been conducted to determine whether one interval is better than the other. The most commonly used version of the self-report questionnaire amongst adult patients, is the Adult AIDS Clinical Trials Group (AACTG) questionnaire (Chesney 2000a). The Paediatric AIDS Clinical Trial Group (PACTG) developed a paediatric adherence questionnaire module (QLW1 p1041 dated 30-01-04) which was piloted and refined during the period 2004–2006. This questionnaire was the self-report instrument used in the present study.

An adaptation of the AACTG self-report questionnaire known as The CASE Adherence Index, was designed and validated by Mannheimer et al.(2006). "The

CASE Adherence Index" is a composite measure composed of three simple questions addressing three different aspects of ART adherence: difficulty taking ART medication on time, frequency of missed ART doses and time since most recent missed ART dose"(p.859). The authors found that this method was highly correlated with the validated AACTG three-day recall self report questionnaire as well as being predictive of virological response.

Another version of the self-report adherence questionnaire was developed, known as Medication Adherence Self-Report Inventory (MASRI), using 12 items with two broad themes(Walsh, Mandalia, & Gazzard 2002). The first section of the questionnaire relates to the medication taken while the second section addressed the timing of doses. Likert scales and visual analogue scales were used as response formats. High self-reported adherence was inversely correlated with viral load.

The **Morisky scale** is an attitudinal questionnaire. It consists of four questions with dichotomous responses and the range of possible responses is 0 to 4. The items are: (1) "Do you ever forget to take your medicine?' (2) 'Are you careless at times about taking your medicine?' (3) 'When you feel better, do you sometimes stop taking your medicine? (4) 'If sometimes you feel worse when taking the medicine, do you stop taking it?' Some of the shortcomings of this tool include the fact that the responses are not time linked with the result that 'non-adherent individuals' rather than non-adherent behaviour are identified. It does not provide information about how many doses have been missed. Inclusion of this information is important since patients with favourable attitudes to treatment, may not be 100% compliant and may miss doses 'accidentally' (Morisky, Green, & Levine 1986).

The Morisky scale was modified by eliminating item 3 since many HIV infected individuals using HAART are asymptomatic; and item 4 was re-formulated to "If at times you feel worse, do you stop taking your medicine?' (Knobel et al. 2002). However, the more important modification was in combining the two approaches outlined above by adding three questions covering dosing behaviour. (1) 'Thinking about the last week. How often have you not taken your medicine?' (2) 'Did you not take any of your medicine over the last weekend? (3) 'Over the past 3 months, how many days have you not taken any medicine at all?' This modified questionnaire is

referred to as the Simplified Medication Adherence Questionnaire (SMAQ). The main purpose of the SMAQ is to identify non-adherent patients. The study also looked at the association thereof with virological outcomes among 3004 adult patients. This validation study demonstrated sufficient internal consistency (Cronbach's alpha 0.75) and satisfactory reproducibility when tested by two different health providers (overall agreement of 88.2%, kappa 0.74). Furthermore, adherence was positively associated with virological outcome in this study.

The evidence for the association between caregiver self-report and virological outcome is conflicting. While some studies found an association between self-reported adherence and a reduction in viral load, others did not. In addition to the studies cited above, Fletcher also found that self-report was a valid measure of adherence and better than pill counts and Haubrich found an association between self-report and viral load ( Fletcher, Pappius & Harper, 1979; Haubrich et al. 1999).

On the other hand, Gao and Nau (2000) highlighted the discordance of the different measures of self-reported adherence. They found the percentage of adherent patients incongruent between the three self-report measures used. For example, among their 65 adult patients, adherence was 29.2% using a Morisky-type scale but 78.5% using a 2-day self-report tool and 95.4% when using a 2-week self-report tool (Gao & Nau 2000).

Measurement of adherence is critical in the management of patients on HAART. Evidence outlined above suggests that a self-report questionnaire is a valid measurement tool but should be interpreted with caution because it may be prone to social desirability bias (Chesney 2000). It is likely that in the context of paediatric adherence caregiver self-report may be subject to this form of bias too, due to the fact that caregivers do not like to be seen as 'negligent'. This assertion is supported by the results from a study which found that adherence (measured by self-report) was significantly associated with the identity of the individual who responded to the adherence questionnaire. The "Full adherence" rate was 47% when the child responded while it went up to 65% when the biological parent responded and still further to 78% when someone other than the child's biological parent responded (Van Dyke et al. 2002).

Amongst adults self-report estimates have been observed to be between approximately 10 and 20% higher than those resulting from pill count data as well as electronic monitoring devices (Bangsberg et al. 2000; Wagner & Rabkin. 2000; Chesney 2000; Liu et al. 2001;Kimmerling, Wagner, & Ghosh-Dastidar 2003).

Yet another form of self-report is elicited using a visual analogue scale (VAS). This is usually a diagrammatic scale representing percentage doses missed over a specific period of time, for example, a 30-day visual analogue scale. The patient has to indicate on the scale their estimate of the percentage pills/doses missed or taken (depending on the investigator's preference. A study conducted in Uganda used a 30-day visual analogue scale whereby adult patients (N=34) had to indicate the percentage pills missed in the past 30 days (Oyugi et al. 2004). They found that VAS results corresponded highly with the other measures in their study such as 3-day self-report, pill counts and MEMS (Pearson's correlation co-efficient of: 0.82, 0.86 and 0.77 respectively). Furthermore, all measures were highly correlated with viral load at 12 weeks.

**Table 2. 1: Types of Self-Report Instruments**

| Instrument | Description | Originator Authors |
|---|---|---|
| **Morisky Scale** | Attitudinal questionnaire consisting of 4 questions with dichotomous responses and the range of possible responses is 0-4. It does not provide information about amount of doses missed. Purpose of the scale is to identify non-adherent patients. | (Morisky, Green & Levine 1986) |
| Simplified medication adherence questionnaire **(SMAQ)** | A modification of the Morisky Scale which includes additional questions regarding dosing behaviour. The purpose of the instrument is to identify non-adherent patients. | (Knobel, et al. 2002) |
| Adult AIDS Clinical Trials Group **(AACTG)** Adherence questionnaire | Direct method of determining number of doses missed in 3 days prior to clinic visit. The main purpose of the instrument is to determine non-adherent behaviour. | (Chesney 2000) |
| Medication Adherence Self-report Inventory **(MASRI)** | Likert scales and visual analogue scales used as response formats. | (Walsh, Mandalia & Gazzard 2002) |
| Paediatric AIDS Clinical Trials Group **(PACTG)** | Module 1- self-report to determine recognition of medication and doses missed in 3 days prior to clinic visit.<br>Module 2 – self-report on reasons for non-adherence | (Watson & Farley 1999); IMPAACT Adherence to Therapy Subcommittee 2000;<br>(Van Dyke et al. 2002) |
| Visual Analogue Scale **(VAS)** | This is usually a diagrammatic scale representing percentage doses missed, over a specific period of time, for example, 30-day visual analogue scale. The patient has to indicate on the scale their estimate of the percentage pills/doses missed or taken (depending on the investigator's preference.) | (Oyugi et.al, 2004); (Muller et al. 2007) |

The administration of the self-report tool is not standard in the sense that some are administered by the health care provider while in other instances they are self-administered. For example, the self-report tool developed by Chesney et al (2000) for the Adult AIDS Clinical trial group was piloted among 75 adult patients on HAART. These tools were self-administered by patients who had at least a sixth-grade level

reading ability (Knobel 2002). The form of administration of the questionnaire may influence the responses.

### 2.5.2. Pill Counts

The simple method of counting remaining pills at a patient's follow-up visit is favoured by clinicians in a routine adult clinic setting. However, these methods are labour intensive and though considered "objective", are presumptive. While pill counts are potentially more accurate than self-report they do not allow one to know whether the medication was actually taken by the patient, nor whether the absence of pills reflects usage. Paediatric formulations add a dimension of difficulty regarding measuring syrups. Measuring instruments and consistency of the syrups may result in measurement inaccuracies. It is also prone to 'wastage and spillage' (the child vomits, spits and fights of administration) thus leading to overestimation of usage and thus adherence. Therefore using this method alone will result in an overestimation of adherence rates in paediatric populations (Patterson et al. 2000; Turner & Hecht 2001).

### 2.5.3. Pharmacy refill records

Pharmacy refill records are often favoured by researchers and clinicians but is usually used in conjunction with other measures such as self-report or pill counts (Ostrop, Hallett, & Gill 2000). Adherence is usually calculated as the total number of refill collections/total number of scheduled collections. The calculation may include the definition of 'on-time' collections e.g. within 2-5 days of scheduled collection date, depending on the estimated number of doses issued.

The review by Steiner & Prochazka (1997) cited forty one HAART adherence studies using pharmacy refill adherence measures. Of the studies that assessed the validity of pharmacy refill measures (which they termed "refill compliance"), most found significant agreement between pharmacy refill and other adherence measures including measures of drug presence (e.g. serum drug levels). However, pharmacy refill adherence was generally higher among drugs with fewer daily doses, and was

inconsistently associated with the total number of drugs prescribed. Despite the above limitations, the authors recommend this method of adherence measure which they indicate is useful in the absence of direct medication consumption measurement. The authors suggested that pharmacy refill records were a feasible measure for population wide surveys.

In a study of HIV infected adults in the US, HAART adherence, as measured by pharmacy refill, was significantly correlated to viral load as opposed to self-report where only in the case of 100% self-reported adherence was there a correlation with viral load (Grossberg, Zhang Y., & Gross 2004).

### 2.5.4. Clinic attendance/ follow-up visits

As with pharmacy refill, scheduled clinic attendance is used as a proxy measure of adherence, although less frequently. Adherence is calculated as the total number of actual visits / total number of scheduled visits during the follow-up period (Natu 2007; Goetz MB 1998; Sorensen et al. 2002). Caregivers who are non-adherent with appointments are more likely to be non-adherent in giving the child medication. In this respect this measure is more predictive in identifying non-adherent than adherent patients (Katko et al. 2001).

### 2.5.5. Electronic Monitoring Devices (EMD)

An electronic monitoring device was first used in 1970 to assess adherence to anti-tuberculosis treatment (Moulding, Onstad, & Sbarbaro 1970). The concept was subsequently developed further by Dobbs and Cramer (Cheung et al. 1998; Cramer et al. 1989). It has been used extensively in research unrelated to HIV, especially to increase adherence to chronic medication among the elderly in the developed world (Kruse et al. 1992).

With the advent of HIV medication, this technology is exemplified by the Medication events monitoring system (MEMScaps). This system involves an electronic chip in the cap of the medication container which records information each time the container

is opened. Results are subsequently downloaded to a computer programme for analysis and results. This technology is expensive and not generally available. It has therefore been used mostly in clinical trials and research settings (Muller 2007;Oyugi 2004; Patterson 2000). The most commonly reported summary EMD measure is the percentage of doses taken. Other common measure include the number of days with correct dosing; percentage days of under or overdosing; percentage of days with correct doses and timing of doses, potentially leading to a more comprehensive picture of the adherence profile of patients.

Researchers are cautioned that whilst this device provides an objective measure of adherence and more valid data than several other methods (such as self-report, pill counts etc.), there are potential pitfalls. These include lack of clarity associated with EMD data and the impact of data management decisions on adherence data reported (Fennie, Bova, & Williams 2006). That is, the device collects longitudinal data on the number of times the container is opened and timing of opening. The underlying assumption is that each opening represents a medication administration event. This may be an erroneous assumption when multiple doses are removed to transfer to pillboxes (while away from home, etc) or the container may be opened without the intention or consequence of taking the medication. The use of pillboxes in conjunction with EMD is a major constraint to the interpretation of data if the clinician or researcher is not informed of this practice. In addition, there may be times when the patient is not responsible for their own medication administration e.g. during periods of hospitalization. Another obstacle is simply the malfunction of the electronic caps, leading to data error. Despite being heralded as the "virtual 'gold standard' for compiling drug dosing histories in ambulatory patients, these methods still have significant limitations (Vrijens, Gross, & Urquhart 2005; McNabb et al. 2003).

### 2.5.6. Physicians' Estimate

The management of HIV-infected patients on antiretroviral treatment is generally clinician-driven although, WHO is advocating 'task shifting' including the increase in the scope of practice of nurses in this regard (World Health Organization 2008).

Physicians' estimate their patients' adherence to medications and base their treatment and management decisions on these estimates. In a system where continuity of care is arranged and valued (as in chronic care clinics), it would follow logically that clinicians have a good idea how their patients are responding to treatment. However, physician's estimates are considered the least reliable method of adherence measurement. Patterson et al reported that physicians predicted patient adherence incorrectly in 41% of cases compared with nurses who only did so 30% of the time (Patterson 2000).

This poor estimation ability is not limited to physicians delivering HIV care as evident in research from the early 1980s. For example, Gilbert et al.(1980) evaluated adherence estimates made by 10 physicians of 74 patients taking the medication digoxin for the treatment of cardiac failure. Adherence was concurrently assessed using pill count and drug serum levels. In this study the physicians only correctly predicted non-adherence 10% of the time. The length of time the physician was caring for the patient had no effect on their low predictive ability: Similar results were found for patients with whom physicians had relationships for more than 5 years.

Several other HIV-related studies have corroborated the finding that physician estimate of adherence is both an unreliable and a poor measure of adherence. In their review of studies on physicians' estimates of HAART adherence, Murri et al. (2002) found discordance between reference measures of adherence (such as pill counts, MEMs, self-report, drug serum/plasma measures) and physicians' estimates, to be between 34% – 45%.

However, two studies were found that conflict with these findings and both were conducted among paediatric populations. Farley et al (2003) found correlation between viral load and Physician/nurse estimates of adherence, while no association was found between caregiver self-report and viral load. Naar-King et al (2006) conducted a cross-sectional study using the average viral load obtained over the 12 months prior to the study to correlate adherence measures and found that physician estimate of adherence correlated with average viral load ($r=-0.39$; $p<0.05$) (Naar-King et al. 2005).

These findings among paediatric physicians may be indicative of the rapport established between patient and doctor due to more frequent interactions or may also reflect different kinds of doctor-patient relationships. Both these studies were conducted in the USA where the rate of paediatric infection is lower than in resource-poor settings and thus paediatric HIV case loads may be much lower resulting in better continuity of care (that is, the patient is seen by the same physician each time).

In summary, despite two studies to the contrary, the evidence suggests that physicians' estimates of adherence is a poor predictor of adherence or non-adherence and thus not feasible as an adherence measure.

## 2.6. Virological and Immunological Outcome Measures

Laboratory outcomes, as assessed by CD4 cell counts and viral load tests are standard biological markers to monitor HIV disease and are often used as proxies for inferring adherence. It should be noted that virological and CD4 count data are used to determine treatment response rather than adherence per se, though it is clear that these are related. The principle is that when the treatment is working, the viral load is reduced to undetectable levels (< 400 copies per ml) and the CD4 count increased indicating reconstitution of immune status. However, in reality response to treatment is more complex than this simple explanation implies. In infants, HAART has been found to be clinically and immunologically effective despite a high rate of virologic failure (Paediatric European Network for Treatment of AIDS 2004).



### 2.6.1. Viral Load Assays (HIV RNA)

Viral loads are traditionally used to assess treatment success or failure and not as a primary measurement of adherence, though it is inferred that the patient is adherent in order to affect viral suppression. A Dutch study among paediatric patients found that virologic failure was associated with poor 'compliance' and younger age of patient, independent of baseline viral load and receipt of pre-treatment (van Rossum, Fraaij & de Groot. 2002).

Many more studies with larger sample sizes have been conducted among HIV-infected adults. However, some of the earlier studies lacked specific measures of adherence and mainly determined clinical outcomes amongst patients on antiretroviral treatment. For example, a study involving 2444 adult patients found that the first few months after initial suppression were the greatest risk period for treatment failure. In addition, patients with a good immunological response were less likely to rebound (those with the lowest levels of viral load-measured to below 50 copies/ml- were significantly less likely to experience virological rebound than those whose viral load was below 400 copies/ml)(Mocroft et al. 2003). One may deduce that those who managed to achieve high levels of adherence in the first few months and thus suppress viral replication were more likely to achieve long-term treatment success. This statement is supported by two studies among adults aimed at 'maintenance HAART therapy' after 3-6 months 'induction therapy'. Results were analyzed for those who did not achieve undetectable viral loads during the induction period and for those who experienced viral rebound to greater than 200 copies per millilitre during the 'maintenance' period. The results showed that patients with rebound had significantly poorer adherence as measured by pill counts and blood levels of Indinavir. The authors concluded that drug resistance may not be the reason for viral rebound and that 'poor adherence (including adhering to dietary restrictions) and sub-optimal anti-HIV drug potency might be factors contributing to viral rebound and inability to reach viral suppression. These study reports underscore the importance of strict adherence to dosing with HAART (Deschamps, Flandre & Calvez 2000); (Havlir et al 2000); (Markowitz 2007).

However, there is evidence to suggest that it is problematic to deduce immediately that a patient on ARV treatment is non-adherent because he/she has virological failure. It is possible to have virologic failure in the face of good adherence. Patterson et.al (2000) demonstrated that adherence was not necessarily directly correlated with virological success or failure. In the latter study, the electronic measuring device (MEMScap) was used to monitor adherence amongst adults. Results showed that 22% of highly adherent patients experienced virological failure and conversely, 18% of those displaying the lowest adherence had undetectable viral load.

Likewise, Steele et.al (2001) found no association between measures of adherence (caregiver report, pill count and electronic cap monitoring devices) and viral load suppression among a paediatric population. The finding of no association may, however, be a result of the study's small sample size (N=34). On the other hand this lack of association may be a function of virological response in children. Young children tend to have high viral loads (Mofenson et al. 1997; Palumbo et al. 1995) and high initial viral load is a risk factor for treatment failure,as measured by viral load suppression (Watson & Farley 1999). The same study suggests that the major impact of treatment is early on in the course of treatment (approx. the first 6 months) and initial viral load response predicts long-term success, regardless of the baseline viral load. However, adherence is but one factor which impacts on achieving undetectable viral load and viral loads may fluctuate even when patients are adhering strictly to treatment. The above evidence suggests that viral load by itself should possibly not be used as a surrogate marker for adherence in infants.

Study findings regarding association between adherence measures and virological outcome have been conflicting. Several researchers report correlations between adherence measures and viral load while others do not (Oyugi 2004). Thus, correlation with viral load is often used to verify treatment adherence measures but correlations are not consistently found.

There are many reasons for these conflicting findings. One of the most critical reasons is variable drug exposure due to variability in adherence, with dose-timing being a fundamental component of drug exposure. For example, secondary analysis by Vrijens and colleagues of the findings of a study by Gross et al. (2001), found that "*changes in viral load were most significantly driven by within-patient dose timing errors"* (Vrijens, Gross, & Urquhart 2005: 227). This aspect is often unaccounted for or ignored in data collection on adherence. However, only the use of electronic measuring devices, lends itself to the collection of accurate dose-timing data as opposed to most other adherence measurement instruments.

## 2.6.2. CD4 cell count monitoring

Immune reconstitution is the goal of HAART, especially in children. As viral load decreases, CD4 cell count is expected to increase. For children, the CD4 percentage is the best measure of immune function and is expressed as a proportion of CD4 cells of the total lymphocyte count (Table 2.2). This is considered preferable for decision-making on antiretroviral treatment initiation. The reason for this is that absolute CD4 cell counts are age dependent and variable, with wide ranges between children. CD4 counts are usually very high in infancy and decline until the age of approximately 6-8 years when it reaches adult values (Paediatric European Network for Treatment of AIDS 1998). The CDC categorizes paediatric HIV disease staging according to clinical and immunological severity using CD4percentage which is less variable, although it also decreases with age (Table 2.2). Monitoring CD4 percentages enables clinicians to monitor disease progression. Data on outcomes of children on HAART in Médicins Sans Frontières Programmes in 12 countries demonstrate that children initiating HAART with CD4 cell % $\geq$ 5% have better outcomes and a greater chance of survival ($\geq$ 80%) (O'Brien et al 2006). However, a study among infants in South Africa, concludes that CD4% is not the overriding predictor of disease progression but that clinical, immunological and virological indicators are three independent predictors of disease progression (Eley et al. 2006).



**Table 2.2: Immunological classification**

| **Immunologic category** | **Age of child** | | |
|---|---|---|---|
| | < 12 months | 1-5 years | 6-12 years |
| | CD4 count μL (%) | CD4 count μL (%) | CD4 count μL (%) |
| 1: No evidence of suppression | ≥1500 (≥25%) | ≥1000 (≥25%) | ≥500 (≥25%) |
| 2: Evidence of moderate suppression | 750-1499 (15-24%) | 500- 999 (15-24%) | 200-499 (15-24%) |
| 3: severe suppression | <750 (<15%) | <500 (<15%) | <200 (<15%) |

Revised human immunodeficiency virus paediatric classification system: immune categories based on age-specific CD4+ T-lymphocyte count and percentage*
*Modified from CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43 (no.RR-12) PP.1-10. Source: (Kline 2004).

In young children (under 2 years) however, the predictive value of CD4 cell percentage for disease progression or death is not high but improves considerably for

children over 2 years. A study among children (aged 2-18 yrs) in the USA found that HAART was associated with increases in CD4 cell counts despite high 'virologic failure'. CD4 cell counts and the proportion of naïve cells were also reportedly higher than in adults. The authors suggest that this may be a reflection of higher thymic activity in children (Essajee et al. 1999). These results indicate that relying solely on CD4 cell outcomes to assess adherence to medication may lead one to erroneous conclusions. It should be noted that CD4 cell count/ percentage is used to monitor treatment response rather than adherence however, the results are often used to imply adherence to treatment. Clearly, this is an erroneous assumption.

### 2.6.3. An Emerging treatment monitoring Tool: Growth velocity

Viral load monitoring is not available in all resource-limited settings. The WHO recommends that where possible, viral load monitoring be conducted at baseline and monitored throughout the course of treatment. The alternative is to monitor clinical outcomes such as growth and health status (World Health Organization 2006d).

A potential indicator for measuring treatment response, specifically in children, is growth. HAART has been shown to have a positive effect on height and weight in children with HIV-1 infection. According to a study conducted in the Netherlands, the positive growth effect is sustained for at least 96 weeks (study duration) in patients who respond virologically to HAART. According to the authors, catch up growth typically affects weight before affecting height (Verweel et al. 2002).

A group from the Duke Clinical Research Institute is also investigating the prediction of treatment failure based on height velocity as a marker for treatment response (Benjamin 2004). In a retrospective cohort study using data from the Paediatric AIDS Clinical Trials Group (PACTG: protocol 300) trial, they developed a clinical predictive model, and compared the utility of the clinical model, to the change in HIV RNA viral load as diagnostic tests of antiretroviral treatment failure. The clinical model incorporated treatment regimen, age, and height velocity. According to the authors the clinical model performed similarly to using changes in viral load. These authors assert that international validation of this tool will render it an 'excellent' low-

cost method for evaluating treatment response amongst children in resource-limited settings. However, the model was tested using data from children in resource–rich settings where growth patterns may differ from those in resource poor settings, where malnutrition and HIV infection may impact differently on growth. In addition, the findings were most pertinent to children aged 36 months and younger who received mono or dual antiretroviral therapy. Thus, this clinical predictive model will need to be tested in resource-poor settings.

## 2.7. Quantitative thresholds for "good adherence"

To date there is no universally accepted definition of patient adherence to HAART as discussed at the beginning of this chapter. Adherence rates are usually treated as continuous variables expressed as percentages. Where adherence is treated as a dichotomous variable, however, researchers use a threshold percentage to differentiate between adherent and non-adherent patients. The quest for the threshold or cut-off point for describing adherent patients has resulted in a range of thresholds from 80% - 100% deemed acceptable in scientific papers (Chesney 2003; HIV/AIDS Project Development and Evaluation Unit 2001; Simoni et al. 2007; Steele et al. 2001). Generally, the tendency is to use $\geq$ 95% doses as the benchmark for adherence (Mills 2006; Weiser et al. 2003; Patterson 2000). This threshold is generally obtained by correlating adherence rates, using various measures, with virological suppression. Across the adult adherence literature it is commonly understood that $\geq$95% of doses (especially PIs) are required to avoid resistance and ensure viral load suppression, hence the threshold of $\geq$95% of doses taken is widely used as a threshold to indicate adherent and non-adherent adult patients (Chesney 2000; Puthanakit et al. 2005; Hansudewechakul et al. 2006; Reddi et al. 2007).

A significant limitation in the review of the literature on paediatric adherence is the fact that it is not possible to establish an overall trend of adherence rates. Studies vary in the methods of adherence assessment, paediatric age groups are not sufficiently stratified (for example, age ranges between 4 months -16 yrs are reported) and various definitions of adherence and thresholds used (Giacomet et al. 2003; Nabukeera-Barungi et al. 2007). In the paediatric adherence literature, the criteria for 'adherent'

and ‘non-adherent’ categories differ in thresholds used to describe adherence. These range from as low as ‘75% of PIs taken’ (Watson & Farley 1999); ≥ 80% of doses taken (HIV/AIDS Project Development and Evaluation Unit 2001); ≥90% of doses taken (Katko 2001) and even ≥93% (Garvie, Lensing, & Rai 2007) , to the most commonly used threshold of ≥95% of doses taken, (Hansudewechakul et al. 2006); (Puthanakit et al. 2005a). Some have used terms such as ‘full adherence’ meaning 100% doses taken (Arrivé et al. 2005; Natu 2007). Thus, a meaningful mean pooled estimate across studies cannot be accurately determined due to the above-mentioned discrepancies.

An attempt has been made to determine estimates of adherence across general HIV-infected populations on antiretroviral treatment. The most recent and comprehensive review of the literature is that of Mills et.al (2006b). They conducted a systematic review and meta-analysis of studies evaluating adherence to antiretroviral therapy (ART) conducted among HIV-infected patients in North American and Sub-Saharan African populations conducted up to April 2006. It should be noted that studies conducted exclusively among children, were excluded from the analysis. A pooled estimate of adherence of 55% and 77% for North American and Sub-Saharan African populations, respectively, was derived. Regrettably, no sub-group analysis was conducted for the paediatric populations within these studies. This is likely due to the paucity of adherence data for this population.

According to a review of literature on paediatric adherence studies, estimates of the proportion of adherent children range from 17% to 100%, in developed country settings and 26% to 98% in resource-limited settings (Vreeman et al. 2007). This review did not include a meta-analysis.

Adherence studies among caregivers of children on HAART in developed countries indicated that non-adherence to treatment is common. A study in the Netherlands among approximately 40 children (ages not reported) found that 38% of children had problems maintaining adherence indicated by virological response (De Groot 2000). Watson & Farley (1999) found 42% of children in their study were non-adherent (less than 75% of Protease Inhibitors (PIs) taken). The Reaching for Excellence in Adolescent Care and Health (REACH) project found significant non-adherence

among HIV-infected adolescents with only 41% reporting "no missed doses" (Murphy et al. 2001).

In contrast, several studies in developing countries report relatively high rates of adherence. In South Africa, Eley et al. (2004) found that between 60-80% of their Cape Town cohort (N=80) achieved ≥95% adherence over a 10-month period. Using MEMScaps, Müller et al (2007) found a 79.5% (N=72) adherence rate amongst their cohort, in Cape Town. A study in Kwa Zulu Natal, reported 89% of the cohort (N= 151 ) achieved >95% adherence(Reddi et al. 2007). Amongst Thai cohorts (N=107), a mean rate of 87% and 90% adherence was reported, respectively, using >95% doses taken as the threshold. (Puthanakit 2005; Hansudewechakul 2006).

Furthermore, 'full adherence' (100%) was reported for 95.4%, 70.5%, 67%, 30% of cohorts in India, Kenya, Côte d'Ivoire, and Uganda, respectively (Natu 2007; Nyandiko et al. 2006; Fassinou et al. 2004; Bikaako-Kajura et al. 2006). These studies demonstrate that a high level of adherence is achievable among treatment naïve paediatric populations in developing country settings and that levels of adherence can be highly variable across different settings. Having said this, these studies did not consistently report correlation of the adherence measure with virological outcome.

The studies reviewed have variable follow-up periods ranging from between 3 months and 24 months, while some are cross-sectional studies (which are inappropriate study designs for adherence monitoring). The metric of estimate of adherence varies between studies. For example, Watson & Farley (1999) expressed the adherence estimate of 52% for the cohort, based on the proportion who "missed more than one dose in the previous 180 days" while Van Dyke (2002) report an adherence estimate of 70% , meaning those who "reported full adherence in the past 3 days". Thus, there is no standardized quantification of adherence or the metric of estimate. However, there is a tendency to report adherence cut-offs above 95% to indicate adherence or to distinguish between "full" adherence and "non full" adherence.

## 2.8. Factors influencing adherence in children

Adherence may be considered a multidimensional concept. Ensuring a constantly high rate of adherence in a routine clinic setting is challenging. The fact that someone starts out being adherent doesn't mean that over time this level of adherence will be maintained by the individual. Non- adherence in an individual increases the risk of the development of resistant virus, rendering the antiretroviral treatment ineffective (Bangsberg, Hecht, & Charlebois 2000). If this resistant virus is transmitted, it will result in the secondarily infected person being resistant to treatment despite being treatment naïve. In addition, non-adherence eventually results in unfavourable health outcomes and increased mortality risk, resulting from immune suppression (Hogg et al. 2000). It is for this reason that clinicians and public health specialists are grappling for the 'best way' to ensure near-perfect adherence to antiretroviral treatment since anything less will jeopardize the nation's long term treatment success.

Identifying the correlates of adherence and implementing evidence-based adherence-enhancing strategies is therefore of primary importance to ensuring treatment success. According to the World Health Organization,

> "The ability of patients to follow treatment plans in an optimal manner is frequently compromised by more than one barrier, usually related to different aspects of the problem. These include the social and economic factors, the health care team/system, characteristics of the disease, disease therapies and patient-related factors" (World Health Organization 2003b:12).

The literature on paediatric adherence to ARV especially among young children is scant especially with regard to the age groups birth to 6 years. A review of literature published during the period 1981-2002 found 12 empirical studies in which adherence to antiretroviral therapy among children and adolescents was a primary outcome measure. Nine of these studies included children under the age of 12 years in their study population. However, median ages of the study populations range from approximately 4 years to 8 years (Steele & Grauer 2003). It should be noted that there are not many studies which have focused on children between the ages of birth to six years exclusively. Only four of the nine studies among children younger than 12

years reviewed by Steel et.al (2003), were designed to identify correlates of adherence, the rest reported estimates of adherence only.

The following section explores the various findings from the literature, relating to factors influencing adherence amongst children as previously outlined above, namely, child, caregiver, Socio-economic and health systems factors will be explored (see Table 2.4 for a summary). It should be noted that in paediatrics the child's refusal to take medication is linked to palatability of medication; hence, this issue will be dealt with under a separate heading, namely Treatment Regimen Characteristics (section 2.8.2), with its related issues such as side effects and pharmacokinetics.

### 2.8.1. Child characteristics

Children differ from adults in their understanding and reactions to illness based upon their level of development. Challenges of adherence facing adolescents are particularly pronounced due to their developmental stage (a time in their lives when they don't want to be different from their peers, being one challenge). Several studies(Ledlie 2001;Goode et al. 2003; Murphy 2001) have reported on these challenges but exploration of factors influencing adolescents is beyond the scope of this review.

It has been suggested that health care providers should assess the influence of developmental factors on adherence periodically and adjust interventions to improve adherence as the child matures (Farley J 2001).

Children generally dislike taking medication and some ARV syrups are unpleasant to taste, making it more difficult to administer as long-term medication. The child's refusal of medicine should not be underestimated as a major factor affecting adherence as revealed in a study among Saudi children (Al-Omran, MacAdam, & Gard 2000). Non-adherence to HAART has been cited as a significant behavioural health problem amongst adults and children alike (Garvie et al. 2003). The phenomenon known as 'pill fatigue/ treatment fatigue' is regarded as the reason for

the decline in adherence over time. This is however, not unique to ARV therapy (Jacobson et al. 1990).

Child factors such as age (infancy, childhood, adolescence) or developmental stage, clinical stage, change in health status, knowledge of HIV status, frequency of school attendance and refusal of treatment have been identified as correlates of adherence (Chesney 2000; Wedekink & Pugnatch 2001; Pontali 2005; Reddington et al. 2000).

An association between treatment adherence and socio demographic factors is not consistently found among studies.

#### 2.8.1.1. Evidence for association between child characteristics and viral load/ adherence

Child age, child's knowledge of his/her HIV status, less depressive symptoms and child stress, decreased child responsibility for medications and improved health status including virological and immunological outcomes were factors which were positively associated with adherence (Belzer et al. 1999;Martinez et al. 2000; Arrivé 2005; Van Dyke 2002; Murphy 2001). For example, with regard to age, Gibb et.al (2003)[11] found that caregivers of children older than 10yrs and those with symptomatic HIV disease were more likely to report full adherence to HAART regimens .

Factors such as severity of illness prior to ARV initiation have been found to impact positively on adherence. A study in Uganda found that no hospitalization or only one episode prior to ARV initiation was associated with poor adherence (Nabukeera-Barungi 2007). This implies that when children are sicker at initiation of HAART, adherence tends to be better, possibly due to the 'Lazarus effect'[12].

[11] The authors were part of the PENTA 5 (Paediatric European Network for Treatment of AIDS) trial which is a randomized, partially blinded, multicenter, comparative study involving HIV-infected children aged 3 months to 16 years who were naïve to ARV therapy.

[12] This is a term which has been popularised in the era of HAART since it describes the dramatic recovery that patients experience who were 'near death's door' when they started HAART and after a few months they were able to resume productive lives.

#### 2.8.1.2. Evidence for no association between child characteristics and viral load /adherence

A study among children in the USA found no significant association between treatment adherence and any of the baseline characteristics such as age at entry into a study, weight, race/ethnicity and gender (Van Dyke 2002). A study in Cotê d' Ivoire found that older child age was inversely associated with adherence (Arrivé 2005).

Several more studies among paediatric populations support the findings that adherence is not related to child's knowledge of their HIV status; nor structural social support, satisfaction with social support and health status including virologic or immunologic outcomes (Martinez et al. 2000;Murphy et al. 2001;Van Dyke et al. 2002; Giacomet et al. 2003; Mellins et al. 2004)

#### 2.8.1.3. Why do studies give such conflicting findings?

The studies cited above, are highly variable in study design, sample size and the wide age ranges studied. It is therefore unclear which studies have the definitive answer as to which demographic factors impact on adherence. It may be possible that these factors become significant under various conditions and that the inability of researchers to control for 'unknown' issues related to the contextual location of the study, has a mediating effect, rendering these variables significant under certain conditions but not under others.

In addition, the few studies among young children lack sufficient power and rigour. For example, among the thirteen studies conducted in resource-limited settings, sample sizes ranged from 40 to 279 with the median sample size of 80 while sample sizes in studies conducted in resource-rich settings ranged from 10 to 129. In addition, prospective study designs provide more rigour for adherence studies. It is encouraging to see that studies emerging from resource-limited settings are favouring this study design, with nine of the thirteen studies employing prospective study designs with follow-up periods between three and thirty four months.

### 2.8.2. Treatment regimen characteristics

Treatment regimen characteristics include: dosing schedule, number and size of pills, taste of liquid or powder formulations, storage and food interactions (Boyle 2000; Pugatch et al. 2002; Fletcher CV 2004).

Palatable formulations do not exist for many available paediatric antiretroviral therapies (ARVs). In paediatric management, dosages can become quite confusing for the caregiver, since dosages are increased as the child grows in height and weight especially for children under the age of 6 years. At each visit, dosages are calculated according either weight or body surface area which could result in a change in instructions to the caregiver regarding the amount of either syrup or tablets the child should receive subsequent to that visit.[13]

Increased amounts of syrups could lead to administration problems due to the fact that it is not particularly palatable and could cause the child to avoid repetition of an unpleasant taste or experience by refusing medication. For example, the dosage of Nelfinavir given in the PACTG 377 study[14] (55 mg/kg BID), meant that an average 6 year old was required to take 5 tablets or 25 scoops of Nelfinavir powder with food, twice a day (Van Dyke et al. 2002).

Paediatric ART formulations are generally supplied in formulations children find difficult to tolerate (viscous and bitter or gritty powders diluted with water or large capsules, which may have to be dispersed in water due to the inability of the young child to swallow capsules). These characteristics do not only pose a problem with palatability for the child but also complicates medication administration for the caregiver (i.e. opening capsules, ensuring mixtures are prepared with clean water, or cutting tablets). While there has been no study that has specifically found significant quantitative results to indicate that palatability is a major barrier, these have been

[13] In the Western Cape Province the use of a standardized weight band/dosing chart was initiated in 2007 by paediatricians at Red Cross Children's Hospital to decrease the frequent dose changes in young children and eliminate the need for complex calculations for dosing.

[14] The PACTG 377 was a multicenter, randomized clinical trial that compared change from current therapy to 1 of 4 drug regimens each of which contained BID stavudine (d4T). A total of 193 children were enrolled into the study.

cited as the most common reasons for 'difficulty in administering' medication (Pontali 2005).

#### 2.8.2.1. Medication Side Effects

There is incomplete knowledge of pharmacology of antiretroviral therapy in children and the effects of nutritional status, age and immunological responses are not well understood or sufficiently documented (UNICEF/WHO Technical Consultation 2004).

Antiretroviral therapy has been associated with short and long-term adverse effects among adults and is an often cited reason for intentional non-adherence (Catz et al. 2000). A Canadian study, aimed at estimating the frequency and possible predictors of intentional non-adherence to HAART, found that 11% of patients enrolled in the study reported intentional non-adherence with between 4% and 7.4% reporting this activity over the preceding year depending on the symptom group.[15] Investigators also found that patients who reported at least one severe symptom were more than twice as likely to report intentional non-adherence and each additional objective side effect that required clinical action was associated with a 25% increase in the risk of intentional non-adherence (Heath 2002).

A few studies among paediatric populations cite side-effects as a reason for missed doses and/ or a barrier to adherence (Temple et al. 2003; Soza-Vento & Fritz 2007). Significant short and long-term adverse events cited among paediatric populations include nausea, rashes, hypersensitivity reactions, lipodystrophy and anaemia as well as long-term toxicities (Pontali 2005; Gibb et al. 2003).

Among fifty seven children aged between 3.8 yrs and 16.8 years and followed up for 48 weeks after initiation of treatment, the most common treatment-related effects, of at least moderate severity, were rash (30%), diarrhoea (18%), neutropenia (12), and biochemical abnormalities (12%). Serious side effects were uncommon (Starr et al. 1999).

[15] 42 different side effects were reported by participants which were grouped by investigators.

Children are reported to suffer the same metabolic abnormalities as a result of HAART as adults which are attributed to Protease Inhibitors (Ramos et al. 2003). The most common metabolic abnormalities encountered by adults are hypercholesterolemia, hypertriglyceridemia and insulin resistance. Other abnormalities include peripheral fat wasting, visceral fat accumulation, and hypertension (McComsey et al. 2003).

In the context of adherence, patients' perceptions of severity of side-effects may differ significantly from the clinical definition of severity, that is, the side-effect may be 'serious' enough for the patient to decide to stop using the medication causing an unpleasant side-effect and thus impacting on the patient's daily quality of life (Adam, Maticka-Tyndale, & Cohen 2003).

#### 2.8.2.2. Pharmacokinetics (PK)[16]

Pharmacokinetics is relevant to the discussion of adherence since the manner in which the body absorbs or excretes the drug may influence its effect on potency and therefore virological outcome.

There's a paucity of data evaluating the pharmacokinetics of antiretroviral treatment in children. Dosage selection for children is often based on insufficient empirical data. With the increased advocacy and pressure for funding of paediatric pharmacokinetic clinical trials, it is envisaged that this matter will be addressed in the near future (Médicins sans Frontières 2006; Global Movement for Children 2006). The lack of paediatric appropriate formulations available, especially in resource-limited settings, result in adaptation of adult formulations by cutting or crushing tablets and dissolving in liquids, which further exacerbates the problem of ensuring adequate dosing in children.

There are unique aspects of paediatric pharmacology as opposed to adults since (1) paediatric dosing is based on age, weight /or body surface area; (2) physiological

[16] PK defined as the study of the bodily absorption, distribution, metabolism and excretion of drugs. (Merriam-Webster's Medical Dictionary,1995)

changes as a result of maturation produces differences in absorption, distribution, excretion and metabolism of drugs (van Rossum et al. 2002).

The majority of the pharmacokinetic data for PIs in paediatric patients has been obtained in older children. However, the ability of an agent to cross the blood-brain barrier may be particularly important when choosing antiretrovirals for paediatric use, since HIV-related encephalopathy is a major problem in HIV-infected children (King et al. 2002).

Inter-individual variability in pharmacokinetics, in general, may produce different effects resulting in some patients having very high drug concentrations, and thus at risk for toxicity, while others with low concentrations are at greater risk for drug resistance and treatment failure. The pharmacokinetics of nucleoside reverse transcriptase inhibitors differ significantly among neonates, infants and older children (King et al. 2002).

Food can increase or decrease the absorption and bioavailability of some drugs and contribute to PK variability. For example, it is recommended that Ritonavir/Lopinavir and Nelfinavir require administration with food for optimal absorption while Didanosine must be given on an empty stomach. In addition, a high-fat or high-protein meal slows the absorption of Zidovudine (Raiten, Grinspoon, & Arpadi 2005).

The current approach supported by WHO of dosing according to weight bands, while expedient for 'demystifying' paediatric HIV management and time-saving, may in fact create more clinical problems in individual paediatric patients. Therapeutic drug monitoring may be indicated in paediatrics. This approach is used extensively in resource-rich countries to optimize dosing in children(Verweel et al. 2006; van Rossum, Fraaij, & de Groot 2002). However, it is not feasible in resource-poor settings where the number of children in need of treatment is escalating rapidly and thus costs of such monitoring will be prohibitive. As a solution, more pharmacokinetic trials are required in these settings to indicate the optimal dosages of HAART in order to prevent treatment failure or toxicity. The results of PK studies conducted in resource-limited settings are not encouraging for the use of adaptations of adult formulations for paediatric use, as is evident from the studies cited below.

These adult capsules were not designed for partial intake and thus this option is far from optimal.

The complexity of drug-dosing in paediatric populations is highlighted by King et.al (2002) when they conclude their findings from a review of PK studies of ARVS among neonates, infants and children compared to adults, by stating:

> "It is imperative that clinicians treating HIV-positive children understand the significance of developmental changes for the pharmacokinetics of antiretroviral drugs, in order to optimize treatment strategies, minimize toxicities and provide the least intrusive regimens for their patients and families" (King et al. 2002: 1132).

The difficulties of dosing in paediatrics, given the limited paediatric-friendly formulations is exacerbated in resource-limited settings where cost drives the choice to compromise, adapting adult formulations in order to give children access to treatment. However, studies are showing that this method of treating children is not optimal. For example, a study in Malawi compared plasma levels of liquid formulations of Nevirapine, Stavudine and Lamivudine with plasma levels of these drugs in children who received divided tablets[17], and compared the bioequivalence of branded and generic formulations of both liquid and tablet products in HIV-positive children. The median age of the children (N= 9) was 7.2 years. The researchers concluded that dosing with a divided tablet is not bioequivalent to using liquid formulations but generic liquid and branded liquid formulations were bioequivalent (Corbett & et al 2005).

More evidence to caution against this practice result from a study in Uganda. The study was conducted to determine the efficacy of using adult formulations adapted for

[17] "The use of quartered tablets for dosing of children has been pursued in African countries because of the lack of availability of liquid formulations in some places and for some drugs. The difficulty in storing and reconstituting liquid formulations, the difficulty in calculating doses of liquids based on body weight and surface area, the higher price of liquid formulations and the widespread use of the fixed dose combination product *Triomune*, which combines nevirapine, stavudine and lamivudine. Medicins Sans Frontieres, for example, has reported that it is far easier to achieve good adherence to quartered tablets in children than it is to ensure that accurate doses of liquid formulation are given consistently" (Keith Alcorn, AIDSMAP, 6 Jan.2006. available at http://www.aidsmap.com/en/news/)

paediatric (by the practice of cut or quartered fixed-dose adult tablets), found poor virological outcomes and high rates of treatment resistance amongst the cohort. Only 59% had virological suppression (<400 copies per ml) at 12 months and this rate declined to 33% at 24 months. Eighty eight percent of those with virological failure were resistant to at least one NRTI and one NNRTI and among these, 28% were resistant to all drugs in the first line regimen. In addition, 30% of children had suboptimal levels of Nevirapine and 20% had suboptimal levels of Efavirenz (Ahoua L et al 2007).

Similarly, a study in South Africa found suboptimal therapeutic levels of Efavirenz in 20% of children their study (Ren et al. 2007). It should be noted that there is no paediatric formulation for Efavirenz in use in South Africa's public health sector and adult capsules are used by opening the capsule and dispersing the contents in water for administration in young children.

These results highlight that the practice of quartered/ cut tablets and dissolving adult dose capsules for dosing in children, according to weight bands, may lead to drug resistance or toxicity because of under or over dosing.

Clearly, the 'science' of paediatric HIV care and Management has several gaps in knowledge. The increased access to treatment, required to stem the tide of perinatal HIV infection still prevalent in Sub-Saharan countries, demands that more focus is given to clinical and pharmacokinetic trials involving children and child-specific issues, since data from adults cannot merely be extrapolated to the paediatric population. Furthermore, these trials should always be underpinned by adherence monitoring.

## 2.9. Caregiver characteristics

### 2.9.1. Knowledge and beliefs about treatment

Adherence is a challenge in children since it depends on the behaviour of the primary caregiver/parent who ensures that the medication is taken. Reddington et.al (2000) found a significant difference between parents of adherent and non-adherent children

regarding their perceptions of their ability to administer the prescribed doses; beliefs about the medication and concerns regarding disclosure of the child's HIV status, indicating that caregiver characteristics impact either positively or negatively on adherence in children. It has been proposed that children maintain better adherence when caregivers believe in the treatment rationale and when the child (when older) can be involved in the decision-making (Chesney 2003). A study by Katko and colleagues (2001) in the USA among a paediatric population with a mean age of 7.5 yrs, suggests that caregivers who are unable to describe the medication regimen were unlikely to adhere to the medication regimen, though this factor, in contrast, was a poor predictor for identification of caregivers who were adherent. Adherence rates in this study ranged from 22 to 100% with only 34% of caregivers giving at least 90% of prescribed medications.

Caregiver knowledge of treatment and self-efficacy[18] positively affects adherence especially in the presence of higher social support and social disclosure of HIV status (Nicholson et al. 2005).

The impact of knowledge of treatment on adherence is highlighted by a study in the USA among a paediatric population ranging in age between 2 and 12 years. They found that significant deficits in caregiver knowledge of regimens and that this was significantly associated with non-adherence resulting in a mean of 49% adherence, based on pharmacy refill which correlated with viral load outcome (Marhefka et al. 2004). Similarly, findings from a qualitative study among caregivers of children on treatment found that adherent patients 'internalized' the knowledge about treatment more strongly than non-adherent; that adherent caregivers had the ability to overcome obstacles to adherence in their children because they believed the benefits of treatment outweighed the difficulties and finally that adherent patients developed better problem-solving capacities. This study further found that the "knowledge,

[18] Caregiver self-efficacy was measured using a scale developed for use by the adult AIDS Clinical Trials Group (ACTG). Caregiver's intentions/confidence in carrying out health-related behaviors (e.g., asking questions, keeping appointments, adhering to medication regimens) was measured using 33 items modified from the Adherence Self-Efficacy Scale. Responses were on a 5-point Likert scale ranging from 0 ''I'm sure I can't'' to 4 ''I can all of the time''. A total score was the mean of responses to all items (alpha = 0.87).

motivation and capacities evolved in a progressive way related to individual stages of coping with human immunodeficiency virus (HIV)" (Hammami et al. 2004:e591)

### 2.9.2. Educational status

The aforementioned findings may be explained by educational status of caregivers as is supported by the results of a study in Saudi Arabia where maternal education was found to be a significant factor influencing health outcomes in children in general(Al-Omran, MacAdam, & Gard 2000).

The impact of caregiver educational level and socio-economic factors is evident in the review of adherence studies among adult patients on HAART, by Fogarty and colleagues (2002). They found at least five studies reporting significant associations between educational level and literacy, lack of stable housing and income and adherence. They report that when an association was found, the direction was consistent in that low literacy, education, income and lack of stable housing, were negatively associated with adherence.

Regarding substance abuse, the above-mentioned authors report that there are as many studies reporting no association, as there are studies which found a negative association and in fact one study documented that those with a history of substance abuse had 'better adherence'! (Fogarty et al. 2002).

### 2.9.3. Caregiver relationship to child

Another factor influencing paediatric adherence is the relationship of the caregiver to the child. The results from the PACTG 377 study suggests that adherence was lower when biological caregivers responded compared to non-biological caregivers ( 65% vs. 78%;p=0.04), respectively (Van Dyke et al. 2002). Consistent with this finding, Katko et.al (2001), reported that the only significant difference in demographic or disease characteristics of patients who had at least 90% adherence was in the proportion of patients for whom the biologic mother was the primary caregiver (p=0.04). Only 8% of children with biologic caregivers had $\geq$90% adherence while 52% of children with non-biologic caregivers had $\geq$90% adherence (Katko et al.

2001). These studies were conducted among paediatric populations in the USA with median age of 6.3 yrs and mean age of 7.5 yrs respectively. These findings may be confounded by the HIV status of the caregiver whereby biological caregivers are more likely to be HIV-infected and possibly not in good health which may result in compromised care-giving ability (Mellins et. al 2004).

To date, these findings regarding biological caregivers have not been verified in resource-poor settings. The results of a Kenyan paediatric adherence to HAART study determined that there was no statistically significant difference in adherence rates between orphaned and non-orphaned children (73% vs. 71%; p=0.86). This was a 34 month prospective study and the median age of the children was 6 years (Nyandiko et al. 2006).

### 2.9.4. Family/caregiver resilience

Families and primary caregivers provide children with information and support that will help children cope with difficult situations. Thus, the family's level of coping will affect the child's psychological adjustment and response to treatment. The literature supports a relationship between the child's ability to cope or adjust to situations and parental stress and distress (Banez GA & Compas 1990; Brouwer et al. 2000).

The literature is not unanimous in its conclusion about the impact of HIV infection on families. Some investigators report that children with HIV and their caregivers evidenced less distress than uninfected children and their caregivers (Bachanas et al. 2001), while others have reported the opposite (Wiener, Vasquez, & Battles 2001; Mellins et al. 2000; Brandt 2007).

The HIV infected individual's ability to cope with stressful life situations have an impact on the ability to adhere to treatment. A Swedish study, which explored the association between self-reported adherence to antiretroviral treatment and degree of sense of coherence (as measured by the 29-item Sense of Coherence (SOC) scale), found that non-adherent patients had lower SOC (p=0.04). They also had lower CD4

cell count/$mm^3$ (p=0.004) and higher viral loads (p=50.02) and that measurement at 12 months predicted non-adherence, the lower the SOC, the more missed doses (p < or =0.01) (Cederfjäll et al. 2002).

### 2.9.5. Socio-economic status and Race/Ethnicity

In Nigeria, socio-economic status (measured by the patient's ability to pay for treatment ) was not associated with adherence (Mukhtar-Yola et al. 2006).

Analyses according to race classification conducted by American researchers have found differences in adherence between groups. A study conducted during the period 1996-1998 among Medicaid recipients found that African-American recipients took longer to commence treatment and were least likely to consistently use the treatment than their White peers. In this study African Americans accounted for 58% of the patients on treatment but 40% of African American patients vs. 30% of White patients reported that they had discontinued their treatment by 1998 (Crystal et al. 2001).

A study conducted in the US among HIV infected children on HAART, found that adherence was less for 'white' than 'non-white children' (40% vs. 73% full adherence) but did not differ between 'black' and 'Hispanic' children(Van Dyke et al. 2002).

In response to assumptions that adherence required for successful ART will not be achieved in resource-poor settings which led to calls for caution in expanded access programs in these settings, a review of studies in Africa demonstrated that this assumption should be refuted. Adherence was found to be "no worse a problem in the described resource-poor cohorts than developed countries" (Orrell 2005: 3). Thus, in resource-limited settings the impact of race/ethnicity should not be a focus of our studies.

### 2.9.6. Gender

If we accept that most caregivers are adults, then reviewing the impact of gender on adult adherence to HAART may be useful in extrapolating caregiver adherence practices in relation to paediatric ARV treatment.

The evidence amongst adult HIV-infected patients shows that gender is not predictive of adherence but there may be specific factors which impact differentially on males and females regarding adherence (Stone 2000;Arrivé et al. 2005; Fogarty et al. 2002). Women (mothers, grandmothers, aunts) are generally the majority caregivers of children. According to Stone (2000), studies have shown that women are more likely to succeed in taking and adhering to HAART when they trust and have an established relationship with their health care provider. Other factors which favour adherence in women are: finding a regimen with minimal or no side effects; when they are provided with the results of viral load levels and CD4 counts coupled with information on their clinical health status and general health issues and have relationships with significant others in their lives such as children, partners, friends or other family. Preliminary results of a survey conducted in the homes of sixty-three HIV positive women on ARVs, showed that women were most likely to report 'unintentional' reasons for missing doses. The best predictor of non-adherence in this group was an inability to describe the effect of antiretroviral medications on viral load that is, their lack of knowledge of HIV and treatment (Durante et al. 2003). This study did not include men and therefore the effect of gender cannot be determined.

It is believed that most women in care-giving roles often neglect their own care at the expense of those for whom they are caring. This belief may lead one to an erroneous assumption that mothers (female caregivers) may ensure better adherence for children on HAART. As previously mentioned above, at least three paediatric adherence studies have reported the converse with regard to biological mothers (Van Dyke et al. 2002); (Katko, Johnson, Fowler, & Turner 2001); (Giacomet et al. 2003). In addition, a Cape Town based study on depression among HIV infected adults which showed that being female increased the impact of negative life events (OR=1.23) and that

increased disability predicted current major depression among this group of patients (OR=1.13)(Olley et al. 2004a).

A study among males (mean age 44.1 yrs) and females (mean age 43.4 yrs) in the USA found higher mean adherence for men than women (79.6% vs. 71.6%, respectively). Factors associated with adherence in males in this study were self-efficacy and intent to follow medical recommendations while practical, (such as 'busy with other things', 'being away from home') rather than cognitive barriers impeded women's adherence. Only perceived barriers was significantly associated with adherence in women (r= -.43; p=0.03). For men, perceived benefit of treatment (r = .36, p< .001), intentions to adhere (r = .39, p< .001), MOS[19] scores (r = .54, p < .001), and age (r = .24, p = .009) were all found to be associated with adherence (Durvasula et.al 2002).

### 2.9.7. Depression

A Cape Town based study investigating psychological adjustment of HIV-infected mothers living in poverty, found that HIV status had a significant, independent impact on levels of depressive symptoms and that HIV infected women 'exhibited significantly more symptoms of depression and anxiety than sero-negative women, regardless of their stage of disease' (Brandt 2007).

Another study among HIV infected adults in Cape Town, found that 56% of the subjects were diagnosed with at least one psychiatric disorder, with major depression being the most common (Olley et al. 2004b).

In psychological discourse, it is commonly understood that hopelessness and negative feelings reduce motivation for self-care. In several studies depression and stress rank among the most significant correlates of non-adherence for HAART (Chesney 2000; Gordillo et al. 1999; Holzemer et al. 1999; Murphy et al. 2001; Patterson et al. 2000). A study investigating the role of psychosocial factors in paediatric adherence to ARV

[19] Perceived social support

therapy, found that higher caregiver and child stress ($p < 0.05$) were more strongly associated with adherence problems(Mellins et al. 2004).

## 2.10. Socio-economic Factors

### 2.10.1. Housing

A study in Cotê d' Ivoire found that there was no association between residential area and adherence (Arrivé et al. 2005). However, housing instability was found to be associated with non-adherence in a study among children and adolescents in the USA (Belzer et al. 1999).

### 2.10.2. Social Welfare

There is a paucity of data regarding the influence of social welfare on adherence among paediatric populations. However, many patients attending public health facilities in South Africa and particularly at the study site have access to the social welfare grants[20].

The Constitution of South Africa grants the right to social services to every child in section 28 (1) (c) and everyone has the right to have access to social assistance if they cannot support themselves and their dependants (section 27(1) (c). For example, the Child Support Grant gives effect to this right to social security (Dutschke 2007).

### 2.10.3. Stigma, Discrimination & Disclosure

Issues such as stigma and discrimination have a major influence on the patient's ability to adhere to HAART. The fear of stigma may prevent the patient from taking medication while away from home to avoid explaining the reason for taking

[20] South Africa allocates a much greater share (3%) of its Gross Domestic Product (GDP) to social grants than any other middle-income or developing country. South Africa's welfare system is considered generous. It provides means-tested non-contributing old-age pensions for the elderly, disability grants for those too ill or incapacitated to work and child support grants for the caregivers of children who are unemployed. (Nattrass 2006)

medication. Stigma and resultant fear of disclosure impact adversely on the patient's ability to take medication outside of the home environment. Studies among adults and caregivers of children found that one of the common reasons given for missing doses were because they were away from home' (Chesney 2003), or visiting relatives or out with friends. Caregivers reported missing doses because they left the child in someone else's care to whom they had not disclosed the child's status (Gibb et al. 2003).

A study in the USA conducted by Reddington et.al (2000) concluded that caregivers' perceptions that adherence is too difficult or concerns about loss of privacy may adversely affect their ability to adhere to complicated medication regimens.

The authors of a Cape Town study among HIV infected adults on predictors of depression, concluded that the significantly higher prevalence rate of depression found in the sample (compared to past community surveys), may have reflected high levels of stigmatization and stress faced by HIV/AIDS patients in South Africa. They further recommended that this finding, regarding stigmatization, should be addressed to ensure adherence to HAART in the context of overcrowded households and perhaps difficult ad hoc child care arrangements resulting in the loss of privacy (Olley, Seedat, & Stein 2004b).



An underlying theme which runs through the literature is the fear of stigma and discrimination which creates a major dilemma for caregivers, children and health care providers around the issue of disclosure of the child's HIV status to both the child and others. In the context of paediatrics, it is difficult to separate the discussion of disclosure of the child's HIV status **to** the child, from discussions about disclosure of the child's HIV status **to others** because caregivers fear accidental disclosure to others by the child (Lesch et al. 2007).

Reluctance to disclose the child's HIV status to the child is more common amongst biological parent/s than amongst other caregivers. A study in Europe across ten paediatric sites, found that among 182 caregivers who responded, 92% were HIV infected and caring for 226 children, of whom 62% were also infected. However, disclosure of either the child's or the caregiver's HIV status to others, was rare and

dependent on the age of the child as well as the relationship of the caregiver to the child. Biological caregivers were less likely to disclose the child's HIV status to the child, than others were. Also, uninfected parents and other caregivers were more likely to want professional help to disclose to the child, than biological caregivers (Thorne, Newell, & Peckham 2000). Behavioural scientists have explained that this phenomenon of biological caregiver avoidance of disclosure, may be a result of parental guilt for infecting the child as well as avoidance being used as a coping strategy (Austin 2003; Keogh et al. 1994).

In the context of paediatric HIV treatment, disclosure to at least **one** other person who may act as a 'secondary' caregiver to the child has become increasingly important as a factor which may influence paediatric adherence. In developing countries, the death toll due to AIDS has left many children orphaned resulting in multiple caregivers taking responsibility for the various needs of the child. Lack of disclosure to a secondary caregiver may result in non-adherence for the child should the primary caregiver be indisposed. In a Ugandan study, lack of disclosure beyond the primary caregiver was found to be a barrier to adherence but that 'complete[21]' disclosure to the child was associated with adherence(Nabukeera-Barungi et al. 2007).

Byrne and colleagues report that in their clinical experience, strong family support and full, early disclosure to the child seems to be important for successful adherence. Furthermore, they found that families who are secretive about the diagnosis among themselves and with the community seem to have the most trouble with achieving and maintaining adherence (Byrne et al. 2002). These observations were supported by findings in a Ugandan study which showed that complete disclosure to the child and strong parental relationships were associated with adherence (Nabukeera-Barungi et al. 2007).

Non-disclosure to children of their HIV status appears common, even in settings where children have been on treatment for a number of years. In an intervention study to improve adherence among children, Berrien and colleagues found that 65%

[21] Complete disclosure was defined as the caregiver reporting disclosure to the child and the child independently reporting that they were told their HIV status.

of the subjects did not know their HIV diagnosis at the beginning of the study. Children who did not know the diagnosis ranged in age between 1.5 to 12 years of age (mean 8.7 years) for the intervention group, and 5 to 11 years (mean 8.4 years) in the control group (Berrien et al. 2004).

In as much as disclosure is relevant to adherence, it is evident that perceptions of stigma and experiences of discrimination will influence adherence to treatment. A study conducted among young adults in Soweto, South Africa found that adherence decreased considerably with fear of being stigmatized by the sexual partner (OR = 0.13 95%, CI 0.02-0.70) (Nachega et al. 2004). However, a fuller discussion of disclosure and its influence on adolescents, important as it is for HIV management is beyond the scope of this dissertation.

### 2.10.4. Orphanhood

The number of HIV infected children who are orphaned, is growing in Sub-Saharan Africa but there is insufficient data on the impact of orphanhood on adherence. Several factors may prevent these children accessing care in the first place, such as non-disclosure of their status and multiple caregivers. However, a study in Kenya found that once in care, no association was found between non-adherence and orphan status (Nyandiko et al. 2006). However, intuitively, we may anticipate many difficulties in South Africa with child-headed households and orphaned children trying to work to support siblings, thus having no 'responsible adult' to take care of them or infected siblings. It is also more likely that children living in these circumstances may only be identified for treatment once hospitalized and then access to treatment may be hampered by difficulty to identify a suitable primary caregiver. Once this person is identified, they may not necessarily be the de facto caregiver which may impact negatively on the child's ability to adhere to treatment.

### 2.10.5. Social Support

Studies have found that factors, such as self-efficacy and perceived social support distinguishes adherent from non-adherent adult patients(Catz et al. 2000). However,

studies among adolescents reported the opposite, that is, that neither structural social support, nor satisfaction with social support was associated with adherence (Murphy et al. 2001).

Reddington et.al (2000) concluded that caregivers of non-adherent children may have had less instrumental social support, indicated by their degree of concern about disclosure of their and their child's HIV status.

## 2.11. Health Service factors

Health Service factors include 'structural barriers' to access to treatment such as distance from the service (transport costs), user fees for medication or medical care and waiting times, which are hypothesized to influence adherence. In addition, the provision of treatment education to the patient/ caregiver prior to initiation of treatment as well as adherence counselling, have been found to impact on adherence (Chesney 2003; Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children 2005; Pontali, Feasi, & Toscanini 2001; Murphy et al, 2001). It has been suggested that this counselling and education takes place within a context which is sensitive to language and cultural characteristics of patients (Shah 2007). Patient–provider relationships were shown to influence adherence and supportive providers help patients overcome barriers to adherence (Chesney 2003). A qualitative study among adolescents reported that creating a strong relationship between the health care provider and the patient before starting treatment was helpful in motivating the patient to remain on treatment (Huba et al. 1997).

In the absence of the identification of specific factors being predictive of change in adherence over time, 'duration on treatment', has been cited as being associated with non-adherence.

An issue which is emerging as critical to adherence, though not framed in this way in the literature, is the fact that HIV infection is a family disease. In the context of paediatric perinatal HIV transmission, this link is even more emphatic. DeMatteo and colleagues brought this fact to our attention in 2002 then they stated:

> "…Surveillance reporting reflects information on infected adults and children but not family groupings. Yet with HIV several family members and multiple generations as well as single or both parents may be infected, highlighting the importance of 'family HIV' as a framework for health policy and programme development. At issue is the problem that medical and other institutions view issues of surveillance, treatment and care through the lens of the infected individual, rather than being family focused. Often it is only in the context of identifying support, or barriers to support, for the medically diagnosed individual that biological or socially created families become a focus of concern. The failure to situate both chronic and life-threatening illnesses within the family setting has serious quality of life and planning consequences for parents and children living with HIV infection as well as other illnesses." (DeMatteo et al. 2002: 278)

The proposal made later in this dissertation, to locate HIV management within the framework of a family-centred- model of care is based on the assumptions outlined above.

## 2.12. Adherence enhancing Tools

Individualized schedules and patient diaries, pillboxes, electronic reminders and clocks and cell phone technology (short message service) have been used as 'patient reminders' to support adherence. It should be noted that patients may have their preference and ultimately what works for a particular patient (as a reminder) should be considered the 'best method'.

A study which tested several tools to remind patients to take their medication and thus improve adherence was conducted among 64 HIV-infected adult patients starting antiretroviral treatment. The study was based on the premise that 'forgetting a dose' is the most common stated reason for suboptimal adherence, indicating a potential benefit of reminder devices (Ostrop, Hallett, & Gill 2000). The tools included individualized schedules, dosettes (pill boxes) and electronic reminder devices. Of the subjects who entered this study, 60.9% (n=39) used at least one adherence tool. It was found that patients who used schedules or dosettes had similarly high rates of adherence (95% and 94% respectively) compared to those who used electronic reminders (76%). This study demonstrates that some of the simple methods, which

are currently practiced in our setting (eg. Pillboxes) are effective tools for improving adherence.

Electronic reminders such as wrist watch alarms and beepers as well as patient diaries have been employed to engage children in medication adherence behaviour (Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children. 2005). However, these strategies are only feasible in resource-rich settings since the cumulative costs to make these available to all patients on HAART are prohibitive in resource-limited settings. Other memory prompting strategies which enable the caregiver or child to utilize triggers in their environment may be more feasible in resource-limited settings.

The cell phone may be a feasible memory prompting strategy even in resource-poor settings. Pilot studies in Cape Town, South Africa found cell phone usage amongst 71% of patients attending public health clinics. The use of cell phone technology to support adherence has been successfully piloted in the TB programme to reduce the load on the DOTS intervention strategy which is the standard of care. This Phone Prompted Self Administered Therapy (PSAT) is a system whereby selected patients are released from the requirement of direct observation and are prompted by the text message service of the GSM (Global System for Mobile Communications) to take their medication daily. Of the 300 patients involved in the pilot there were only five treatment failures, and WHO has singled out the scheme as an example of best practice (World Health Organization 2003c).



## 2.13. Interventions to improve paediatric adherence

There is a paucity of published data relating to interventions aimed at increasing paediatric adherence to HAART especially in children younger than six years of age. In their review, Simoni and colleagues only found eight studies which were mainly small feasibility or pilot investigations, investigating paediatric adherence-enhancing interventions (Simoni et al. 2007). The present review identified nine empirical intervention studies.

The limited literature on paediatric adherence to antiretroviral treatment reviewed above, suggests that non-adherence is influenced by characteristics of the child such as developmental stage, the inability to swallow pills or refusal to take medication. Caregiver characteristics which influence adherence are drug use, health status, stress and coping ability, health beliefs, lack of social support. The characteristics of the health care provider which influence adherence are: patient dissatisfaction with care, provider perceptions of patients' ability to adhere to treatment and the medication. Medication characteristics such as unpleasant taste, complexity of regimen, that is, the number of pills/medication to be taken, food stipulations and dosing requirements, further impact on adherence. Interventions therefore need to be aimed at identifying deficits, which may involve any one of the above-mentioned areas and be context specific or multifaceted. Among young children who rely completely on adult caregivers for the medication, issues directly relating to the caregiver, need to be explored for intervention.

Caregivers surveyed in one study felt that the most helpful interventions for improving adherence would be modifications to medications to improve convenience and palatability as well as increased access to medical advice(Reddington et al. 2000). The authors have further suggested that support for adherence should be tailored to the individual family's needs and while a variety of interventions should be made available, this support may be less necessary with the development of more convenient dosing and palatable medications. This suggestion however, implies that the most significant barrier to paediatric adherence is related to the medication characteristics. This view is too simplistic as illustrated by the range of factors shown to impact on adherence in the present review.

A summary of interventions is tabled in Table 2.3. The results of the interventions indicate minimal impact in most instances, considering the amount of resources invested in the interventions. However, it should be noted that most of the interventions were apparently 'as a last resort measure', that is, children who were consistently non-adherent or had unsuppressed viral loads over time thus probably the most likely cases to fail. Several factors were identified to impact on adherence in the process of these interventions outlined below.

The various types of interventions are outlined below with most of the interventions modelled on the 'directly observed therapy' (DOT) model. Most of these DOT interventions were conducted via hospital admission including invasive procedures such as gastronomy tubes. This increases the cost of this type of intervention which can be prohibitive in resource-limited settings where in-patient beds are limited for very sick children and thus clinically well children will be very low on the priority list for hospitalization. There are few researchers who have conducted a cost analysis of paediatric HAART adherence interventions (Cunningham et al. 2006; Hansudewechakul et.al. 2006).

Interventions to enhance paediatric adherence to HAART either focus on skill enhancement relating to medication administration among children and caregivers or on knowledge, behaviour and psychosocial influences or a combination of these approaches.

### 2.13.1. Patient Education

A study involving home visits by nurses focused on HIV/AIDS information/education and resolution of barriers to adherence in the home environment in the USA. Pill counts were also done by nurses during home visits the purpose of which was to "point out success or misconceptions about treatment". This was a randomized controlled intervention design with patients (N=37; 20 intervention and 17 controls) either randomized to either the home intervention or control group. The results indicated that while knowledge and refill history improved significantly in the intervention group in the, the impact of this intervention on viral load and CD4 counts were reportedly minimal. However, improvement in adherence was associated with improvements in CD4 and viral load outcomes even after 6-11 months after the intervention. Mean pharmacy refill score was 2.7 in the intervention group and 1.7 in the control group; $p < 0.002$ and slight improvement in self-reported adherence was noted in the study group (Berrien et.al. 2004).

In another 'patient education' intervention, a system of ongoing HIV education and care training for children and caregivers was established in Chiang Rai Hospital, Thailand to improve adherence among children. An evaluation of the intervention

involving 57 child-caregiver pairs was reported. The intervention involved pre-HAART education and discussion of critical issues such as disclosure, adherence for 1 day. Children and caregivers were targeted with children's training involving the choice of a DOT supervisor (1 or 2 adults); medication reminder tools & adherence support materials (self-record diary, weekly pillboxes and wristwatch). Caregiver training involved drug preparation (cutting of tablets and administration tips) as well as guidance on how to implement DOT with emphasis on being supportive and non-judgmental. The duration of the intervention was as follows: Pre-HAART initiation (1 day education at health facility); 1 home visit by nurse 3 days after initiation; one day education on Day 14 and once a month for 6 months; thereafter once every 3 months. Adherence measures were taken at these visits.

The results showed that ninety percent of children (N=110 with median age of 9 yrs) achieved >95% adherence in the first six months compared to 87% in the subsequent 6 months. However, results showed that no single intervention was associated with strict adherence over time (>12 months)(Hansudewechakul 2006). Two factors found to negatively impact on adherence during the first 6 months, but not in the subsequent 6 months, were, being cared for by a grandmother and older age of children (above the mean of 9.3 yrs (p=0.05).

The cost of this intervention was estimated at approximately $25 per child per month.

### 2.13.2. Patient education regarding clinical practice to avoid potential barrier: An example.

Interim results from the Children with HIV Early Antiretroviral Therapy (CHER) study suggest that giving ARVs to children as young as six weeks old, irrespective of immunological or health status, results in reduced mortality. One of the aims of the study was to determine whether early initiation of treatment for a limited period (1 or 2 yrs) could be beneficial to facilitate the building of the infant's immune system in order to delay disease progression. The trial was underway at the time of writing (Violari et al. 2007).

The implications of this study are that paediatric treatment protocols may be revised with guidance from WHO in the following: very young children who test positive for HIV infection, *irrespective of health status*, will be given ARVs at diagnosis. In the light of the evidence from the present adherence study which illustrates the complexities of medication administration and paediatric adherence, the implementation of such recommendations should be approached with caution by ensuring that caregivers are adequately prepared for this event. There may be several factors which may impact on biological mothers' decisions to continue ARV treatment once they leave the health facility. Such decisions may hinge on issues such as denial of the child's HIV status or having the perception that the child is not 'sick' enough to warrant ARVs or needing to consult with significant other people in their lives such as partners and elders. The public education around ARV treatment to date is that not everyone who is HIV infected requires antiretroviral treatment. The 'new' approach to treating all HIV infected infants will require public awareness of the reasons why this differs from the main message regarding antiretroviral treatment.

### 2.13.3. Directly Observed Treatment

An intervention was conducted to determine whether prolonged detectable viral load could be attributable to poor adherence. The researchers demonstrated that directly observed therapy administered for as little as four days (4 children in hospital and 2 at an HIV programme sponsored summer camp) in children aged between 3.3 and 11.5 years was successful in lowering viral load by as much as 70% (0.5 $\log_{10}$ drop in viral load ) (Gigliotti, Murante, & Weinberg 2001).

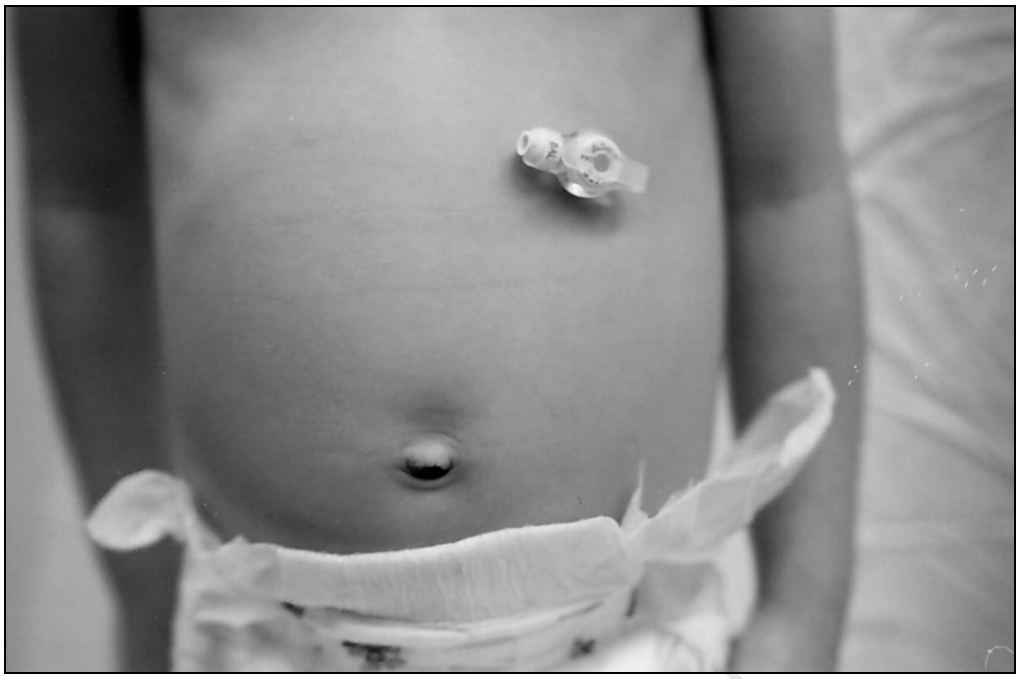
However, for Roberts et al. (2004) employing an 'Enhanced DOT' strategy for six families of children with constant detectable viral loads over many years did not yield as successful an outcome. Their approach involved an initial referral to a home health nurse who visited families in their homes and then DOT (during a four day hospitalization) supplemented by hospital based caregiver training and at two weeks post-discharge. There results showed no sustained improvements in adherence except in the two cases reported for medical neglect that were later placed in foster care with improved virological outcomes. However, it should be noted that the criteria for

participation in this intervention were children who had not had virological suppression 'for years' and thus were most likely to face several barriers to adherence. In Cambodia, 117 children with 'late stage' HIV-infection, in a village were administered DOT HAART by Child Care Workers working for a NGO for a period of six months. An evaluation of outcomes showed that 22(18%) died within the first 6 months and CD4 counts increased substantially for the rest over a 6 month period (Myung et al. 2007).

### 2.13.4. Gastrostomy

For families who demonstrate poor adherence because they struggle with medication administration due to the child's inability to swallow, or constant vomiting of medication etc, gastrostomy tube insertion may be the appropriate intervention (in combination with behavioural therapy or clinical intervention, depending on the cause). A one year retrospective chart review found 17 children who had gastrostomy tube insertions for improvement of medication adherence (Shingadia et al. 2000). Ages ranged from 1.25-11.8 years with a median age of 2.9 years. The intervention was reportedly successful with all 17 patients described as "adherent" on their charts, one year after the procedure. However, only for 10 children was a $\geq$2-log reduction in viral load found. Co-incidentally, these 10 children all had a regimen change at the time of the procedure. It is hypothesized that the regimen change minimized the impact of viral resistance secondary to non-adherence. Furthermore, caregivers found the devices acceptable and reported reductions in medication administration time and improvement in child behaviour during medication administration.

**Figure 2. 1: Gastronomy Tube button on a child's abdomen.**



Source: Shingadia et.al. (2000) PEDIATRICS Vol. 105 No. 6 June 2000, p. e80



### 2.13.5. Multi-systemic Therapy

Though the present review does not focus on adolescents, this intervention deserves mentioning since it could be used for younger age groups, despite its prohibitive cost. The young child is utterly dependent on the family and caregivers and usually reflects the dynamics in the household and related social systems, in their behaviour.

An intervention approach currently being explored for adolescents infected with HIV and non-adherent to treatment in the USA, is called "Multisystemic Therapy" (MST). According to (Cunningham et al. 2006: 45 this is "an empirically supported, comprehensive community-based treatment for adolescents presenting serious clinical problems (e.g. Violence, drug abuse) and their families".

This approach has recently been adapted to improve adherence and health outcomes in urban youths with chronically poorly controlled type 1 diabetes and piloted among HIV infected children (Ellis et al. 2004). In the afore-mentioned study , 19 children

aged 1-16 years participated with significantly decreased viral load from referral to end of treatment, persisting to 3-month follow-up. An interesting finding of this study was that caregiver –reported adherence did not change as a result of the intervention. This intervention required 46 therapy sessions over 7 months and may not be feasible in resource-limited settings.

The treatment theory underlying MST draws on social-ecological and family systems theories of behaviour. The approach involves mental health specialists who work with a youth and his family at the community level (school, home). They conduct home visits approximately three times a week over a period of 6 months. During the intervention cognitive-behavioural therapy and structural family therapy is provided to effect change within and between the systems in which the youth operates and that directly or indirectly influenced the non-adherent behaviour. However, this is a prohibitively expensive intervention (especially for resource-limited settings), costing approx. $5500-$6000 per case (Cunningham et al. 2006).

### 2.13.6. Pill Swallowing Training

Due to the lack of appropriate and suitable ARV formulations for children, it is believed that simplification of children's doses (eg. By taking it in pill form, thereby reducing the volume of unpleasant medication), may lead to better adherence. Garvie and colleagues conducted a retrospective patient chart review of 23 paediatric patients aged 4 to 21 years who referred for pill-swallowing training by an experienced paediatric psychologist over a period of two years. An explanation is not given in the publication for the inclusion of young adults up to the age of 21. Mean age at referral was 7.9 years.

Patients (N=23) participated in individual training sessions in which the appropriate swallowing technique first was modelled by the trainer (the clinic paediatric psychologist), then practiced by the child. The child practiced using pieces of gummy worm candy cut to size to emulate commensurate placebo gel cap sizes before making the transition to lactose-filled placebo gel caps. These were swallowed in gradually increasing sizes. Successfully swallowing two of each placebo size with ease was

required before progressing to the next size. The number and the length of sessions were determined by the individual patient's rate of progress. The target gel cap size was dictated by their prescribed or desired treatment regimens. Each child participated in as many sessions necessary to achieve success (e.g., reach target pill size) or until it was determined that the child was not developmentally ready to acquire the skill. In general, sessions lasted between 15-30 minutes.

**Table 2.3: Empirical Interventions to improve Paediatric Adherence to HAART**

| Intervention Description | Results | Authors |
|---|---|---|
| "**Home based intensive nursing intervention**<br><br>**Duration:** 8 structured sessions over a 3 month period.<br><br>**N=37** (20 intervention and 17 controls) | HIV knowledge and adherence (measure by pharmacy refill) increased in study group (mean refill score was 2.7 in the intervention group and 1.7 in the control group; *p* _ 0.002).<br>Improvement in adherence was associated with improvements in CD4 and viral load outcomes even after 6-11 months after the intervention. The authors speculate that the experienced home care nurse was key to the success of the intervention. | (Berrien et al. 2004)<br><br>**Country**: USA |
| **HAART initiation and treatment support intervention:**<br>Involved pre-HAART education and discussion of critical issues such as disclosure, adherence etc.(1 day)<br>**Duration (12months):**<br><br>**N=57** | During first 6 months, 90% were 'strictly adherent. Between 6-12 months, 87% were strictly adherent.<br>Use of adherence tools declined over time but was not significantly linked to a decline in adherence.<br>As-treated analysis showed that, at 6 and 12 months of therapy, 64% and 61% had a viral load < 50 copies/ml, and 94% and 93% had < 400 copies/ml, respectively as opposed to Intent-to-treat analysis which showed that, 53% and 58% had a viral load < 50 copies/ml and 77% and 88% were <400 copies/ml, respectively. | (Hansudewechakul et al. 2006)<br><br>**Country** : Thailand |
| **A short course DOT intervention**<br>**Duration**: hospitalization over 4 days<br>(2/4 had DOT administered at HIV sponsored summer camp. N=6 children | Children aged between 3.3 and 11.5 years. DOT "by hospitalization" was successful in lowering viral load by as much as 70% (0.5 $\log_{10}$ drop in viral load ) | (Gigliotti, Murante, & Weinberg 2001)<br><br>**Country**:USA |
| **DOT (Multidisciplinary In-patient care)**<br>**Duration**: Length of stay for each patient was not reported.<br>After discharge, the patient was seen weekly in the outpatient paediatric clinic for viral load and adherence monitoring.<br><br>**N=21** (23 hospital admissions) | A retrospective analysis of the data revealed that the intervention resulted in an immediate and sustained (up to 6 months) reduction in viral load and increase in CD4 count. Mean age of participants was **12.6 years**. Over half of the patients in the study maintained 1 $\log_{10}$ or more decrease in viral load 6 months after discharge. Additionally,<br>more than one third of patients in the study attained an undetectable viral load by 6 months after discharge. | (Parsons et al. 2006)<br>**Country**: USA |

| | | |
|---|---|---|
| **Enhanced DOT intervention**<br>**Duration:** four day hospitalization + home health nurse.<br>(2 cases were referred to the state authorities as 'neglect' due to un co-operation from caregivers).<br><br>**N= 6 families** | The results showed no sustained improvements in adherence except in the two cases reported for medical neglect, which were later placed in foster care with subsequent improved virological outcomes. | (Roberts et. al. 2004)<br>**Country**: USA |
| **Community based DOT**<br>Child Care workers employed by an NGO, administered DOT to children, twice a day.<br>**N=117** | 22(18%) of the children died within the first 6 months. CD4 count increases reportedly comparable to those found in US and European studies (but not specified). Staffing costs estimated at $5 per child per month. | (Myung et al. 2007)<br>**Country**: Phnom Penh, Cambodia |
| **Gastrostomy Tube Insertions.**<br><br>A one year retrospective chart review of children who had gastrostomy tube insertions for improvement of medication adherence<br><br>**N=17** | Ages ranged from 1.25- 11.8 years with a median age of 2.9 years.<br>The intervention was reportedly successful with all 17 patients described as "adherent" on their charts, one year after the procedure. A $\geq$2-log reduction in viral load was only found in 10 children. It should be noted that authors report that these 10 children all had a regimen change at the time of the procedure. | (Shingadia et al 2000)<br><br>**Country**: USA |
| **Multisystemic Therapy (MST)**<br>**Duration:** This intervention required 46 therapy sessions over 7 months.<br><br>**N=19** | Children aged 1-16 years participated with significantly decreased viral load from referral to end of treatment, persisting to 3-month follow-up. An interesting finding of this study was that caregiver –reported adherence did not change as a result of the intervention. | (Cunningham et al. 2006).<br><br>**Country**: USA |
| **Pill Swallowing Training**<br>**Duration:** The number and the length of sessions were determined by the individual patient's rate of progress. or until it was determined the child was not developmentally ready to acquire the skill. In general, sessions lasted between 15-30 minutes.<br>**N=23** | Modal number of sessions required to acquire the pill-swallowing skill was 1 session. Younger children (aged 4–5 years) required a median of 2 training sessions, and older children required 3 sessions.<br>A significant improvement in adherence from baseline to 6 months post–pill-swallowing training completion was observed, as were significant related improvements in CD4_ T-cell% and viral load.<br>. | (Garvie, Lensing, & Rai 2007)<br><br>**Country**: USA |

## 2.14. Conclusion

The term "adherence" in the context of HIV medication is not clearly defined. As a result, evaluation of adherence is subject to the evaluator's definition and standard, resulting in relative 'successes' of interventions to improve adherence. However, there is a common understanding of the parameters required to evaluate HAART success, namely, virological suppression, immune reconstitution, correct dosing and administration of medication with minimal or no side-effects. However, virological suppression is considered the alternative 'gold standard'[22] and goal of HAART.

Several methods are employed to measure adherence. By far the most common method of adherence assessment found in the literature is a subjective method of 'self-report' and in the case of young children "caregiver self-report" using the range of self-report instruments, including, to a lesser extent, visual analogue scales. However, electronic monitoring devices are commonly used as a reference measure in research studies in the developed world but are not yet widely used in resource-poor settings though there are a few exceptions (Müller et al. 2007; Oyugi et al. 2004).

The literature regarding paediatric HAART adherence, is limited, especially in the very young. It is not easy to extract data regarding ages among the study populations but there seems to be a trend towards studies with higher age groups with median ages ranging from 4 to 12 years and mean ages reported from 2.6 to 9.8 years.

This chapter has summarized the factors influencing adherence into four domains namely, child factors including treatment characteristics, caregiver factors, health service factors and Socio-economic and social factors (see Table 2.2[23]). From the above literature, it is obvious that the factors influencing adherence are not fixed in relation to being either barriers or facilitators of adherence. This is true for both adult focused studies and the paediatric focused studies. There is a need to continue to

[22] Pharmacologic measurement of plasma concentrations of the various antiretroviral agents is the 'gold standard' for objective measurement of adherence. However, it is not routinely available commercially and is prohibitive in terms of cost.

[23] Note: Table 3 summarizes the factors as is evident from studies conducted among paediatric populations only.

explore these factors and to identify those factors influencing specific patient cohorts, taking into account the contextual setting of both the service and the patients.

Furthermore, it was illustrated by the review on empirical interventions to improve paediatric adherence to HAART that proactive interventions such as patient education and skills training at HAART initiation may be more successful than interventions introduced long after barriers to adherence have become entrenched in the patient and family system.

It may therefore be wise to pause and consider the proposal of Vrijens and colleagues to create an explicit discipline within biopharmaceutics concerned with "what the patient does with the drug" in addition to the other two, namely, pharmacokinetics (what the patient's body does to the drugs) and pharmacodynamics (what the drug does to the patients body).



They have coined the term "Pharmionics" to describe this sub-specialty. They argue that:

> "Pharmionics is the discipline concerned with the ways in which prescription drugs ''go'' into use – in the broadest sense of the word ''go''. This new field subsumes matters that meant little when prescription drugs had little therapeutic power, and were usually used singly rather than in complex combinations. Pharmionics has gained in importance as drugs have gained in both therapeutic strength and potential for harm if misused (p.227)(Vrijens, Gross, & Urquhart 2005).

This review has identified several studies providing paediatric adherence data which are incidental to another line of investigation and therefore not rigorously collected nor measured. This proposed approach to the study of adherence (recognising it as a focussed discipline called 'Pharmionics') may provide the impetus for provision of resources to enable methodologically sound and more rigorous studies which include the younger paediatric population in general biopharmaceutics and in HAART research, in particular (notwithstanding ethical dilemmas of research in young children, the discussion of which is beyond the scope of this dissertation).

The present study will therefore add to the body of knowledge regarding adherence among a very young group of paediatric patients attending public health facilities and living in resource-limited settings.

Until the point of implementation of the present study (October 2004), no other studies could be found in the published literature which focused on adherence measurement and factors influencing adherence among non-school going children in resource-limited settings. Most studies published in resource-limited settings prior to 2004, focused mainly on the clinical outcomes of antiretroviral treatment with adherence being incidental to the main clinical focus.

Four measures of adherence are compared in the present study, namely, caregiver self-report, pharmacy refill, clinic visits and medicine measure/pill counts. The choice of these measures was motivated by the search for an appropriate measure of adherence, for use in a routine clinical setting.

**Table 2.4: Paediatric Adherence to HAART in resource limited settings**

| No | Study | Self-report | Pharmacy | Clinic | Pill Count | Factors Reported (Y/N) | Factors |
|---|---|---|---|---|---|---|---|
| 1. | (Nabukeera-Barungi et al. 2007)<br>Uganda<br>Cross-sectional study | 89%<br>3-day recall | NIL | NIL | 94.1(clinic based counts)<br>72%<br>(unannounced home counts) | **Yes** | Yes<br>Disclosing the child's HIV sero-status only to the primary caregiver and having been hospitalised only once or not at all were associated with poor adherence. |
| 2. | (Natu & Daga 2007)<br>India<br>(6-month Prospective study.) | NIL | NIL | 95.4% | NIL | **No** | |
| 3. | (Arrivé et al.2005)<br>Cote d'Ivoire<br>Cross-sectional study | 67%<br>30-day recall | NIL | NIL | NIL | **Yes** | Older child age associated with non-adherence. No significant difference was found for characteristics such as gender (P = 0.236), parent status (P = 0.095), median age at study period (P = 0.162), home place (P = 0.230), and medications taken during the study period: Zidovudine (P = 0.072), Stavudine (P = 0.072), Didanosine (P = 0.902), Lamivudine (P = 0.902), Efavirenz (P = 0.413), and Nevirapine (P = 0.413). |
| 4. | (Bikaako-Kajura et al. 2006)<br>Uganda<br>Cross-sectional study | 29% No missed doses<br>40% occasional<br>(qualitative) | NIL | NIL | NIL | **Yes** | Overall, 12 (29%) of the children and their caregivers reported excellent adherence (never missed any).<br>dose), 17 (40%) good adherence (occasionally missed doses) and 13 (31%) poor adherence (frequently missed doses). Complete disclosure and strong parental relationships were related to good adherence and ART at the Mildmay Centre in Uganda. |
| 5. | (Hansudewechakul et al. 2006)<br>Thailand<br>12 month | 90% (1st 6 months)<br>87% (next 6 months) | NIL | NIL | NIL | No | |

| No | Study | Self-report | Pharmacy | Clinic | Pill Count | Factors Reported (Y/N) | Factors |
|---|---|---|---|---|---|---|---|
| | Prospective study | | | | | | |
| 6. | (Puthanakit et al. 2005)<br>Thailand<br>18 month<br>Prospective study | not reported separately reportedly used in conjunction with pill counts | NIL | NIL | 86% | No | No factors influencing adherence reported only that Treatment regimen and adherence are associated with virological success. |
| 7. | (Nyandiko et al. 2006)<br>Kenya<br>34 mth Prospective study (median age 6 yrs) | 75% | NIL | NIL | Not reported, though measured. Also clinicians' estimation of adherence measured but not reported in results. | Yes<br>Impact of orphanhood | Perfect adherence among children with known orphan status was 75% and was not significantly different between orphaned and non-orphaned children, 73% versus 71%, respectively (P = 0.863). Orphan status was not a significant predictor of death (P = 0.836) or loss to follow-up (P = 0.096). |
| 8. | (Muller et al. 2007)<br>Cape Town, SA<br>6 month Prospective study | CG-VAS<br>98.6% | NIL | NIL | MEMS mean of 79.8% with 68% taking doses within 1 hr of prescribed time | No | Factors not reported |
| 9. | (Fassinou et al. 2004)<br>Cote d'Ivoire<br>21 month<br>Prospective Study | 70,5%<br>qualitative interviews by psychologist | NIL | NIL | NIL | No | |
| 10. | (Eley et al. 2004)<br>Cape Town, SA<br>10 month prospective study | NIL | NIL | NIL | 60%-80% | No | |

| No | Study | Self-report | Pharmacy | Clinic | Pill Count | Factors Reported (Y/N) | Factors |
|---|---|---|---|---|---|---|---|
| 11. | (Reddi et al.2007) KZN, SA 1 yr Retrospective study | 89% | NIL | NIL | NIL | No | |
| 12. | (Mukhtar-Yola et al. 2006) Nigeria 6 month prospective | 80% | NIL | 87% (on-time) | NIL | Yes | The social class of the patients did not significantly affect their level of adherence. Even though cost was identified as a barrier to treatment in our patients, those from the middle and lower social class who were able to buy their medication were just as adherent as patients from the upper social class. Side-effects did not pose a barrier to adherence in this study. |
| 13. | (Pensi 2007)1) India 12 month prospective study | 100% reported >95% adherence | NIL | NIL | NIL | No | |

**Table 2.5: Factors influencing Paediatric Adherence**

| Domain | Variable | Evidence from Studies | Citation |
|---|---|---|---|
| **Child Characteristics** | Age/ developmental stage | ▪ Older age impacts negatively on adherence<br>▪ Age (children > 10 years) associated with adherence (p=0.04)<br>▪ No impact of age on adherence using two cut-offs (> 8 yrs and < 8 yrs)<br>▪ Younger child age related to better adherence<br>▪ Child age unrelated to adherence<br>▪ Social and emotional development influences adherence due to child's ability to self-regulate his/her perceptions of illness. | ▪ (Arrivé et.al 2005) Cote d'Ivoire; (Mellins et al, 2004) USA<br>▪ (Gibb,et al. 2003) Europe<br>▪ (Giacomet et al. 2003) Italy ; (Van Dyke, 2002) USA<br>▪ (Garvie et al. 2003) USA<br>▪ (Martin et al. 2007) USA; (Martinez et al. 2000) ; (van Rossum et al. 2002) Netherlands |
| | Gender | ▪ No impact of gender on adherence | ▪ (Giacomet 2003) Italy ; (Van Dyke et al. 2002) USA |
| | Child behaviour | ▪ child's refusal to take medication is a major barrier to adherence (also see comments under Medication characteristics)<br>▪ Children sleeping through dosing times, cited as reasons for missing doses<br>▪ Decreased child responsibility for medication impacts positively on adherence | ▪ (Al-Omran, MacAdam, & Gard 2000) Saudi Arabia (also see under 'medication characteristics'<br>▪ (Mukhtar-Yola et al. 2006) Nigeria |
| | Child's knowledge of HIV status | ▪ Children (older than 8yrs) aware of their HIV status were less adherent<br>▪ Complete HIV disclosure to children and strong parental relationships promote good adherence (*NB 50% of cohort | ▪ (Giacomet et al. 2003) Italy<br>▪ (Bikaako-Kajura et al. 2006) Uganda<br>▪ (Van Dyke et al. 2002) USA |

| Domain | Variable | Evidence from Studies | Citation |
|---|---|---|---|
| | | were orphaned).<br>▪ Child's knowledge of HIV status did not affect adherence | |
| | Health status (improvement or deterioration) | ▪ No hospital admissions or only one associated with poorer adherence<br>▪ Clinical features (immunological status or stage)have no impact on adherence<br>▪ Children with more advanced disease are more adherent | ▪ (Nabukeera-Barungi et al.2007) Uganda<br>▪ (Giacomet 2003) Italy; (van Rossum et al. 2002) Netherlands<br>▪ (Gibb et al. 2003) Europe (PENTA) |
| | Orphan status | ▪ No significant difference in adherence between orphans and non-orphans (73% vs. 71%)*(NB. to be interpreted with caution, there was significant loss to follow-up among orphans in this study) | ▪ (Nyandiko et al. 2006) Kenya |
| **Medication Characteristics** | Medication characteristics (linked to child behaviour with regard to 'unwillingness' to take medication)<br>**Characteristics**: taste, palatability, size of pills, availability of liquid formulations, storage requirements (refrigeration of liquid formulations), adverse effects as well as<br>PK properties: frequency of dosing, dosage, dietary restrictions, drug interactions. | ▪ Medication characteristics, a barrier to adherence resulting 'unwillingness' to take medication<br>▪ Frequency of doses has an inverse relationship with adherence.<br>▪ More complex regimens (≥4 drugs)found to correlate with better adherence (postulated that these children were sicker and thus more likely to take meds)<br>▪ Higher 'pill burden' (4-drug) vs. (3-drug) regimens associated with non-adherence | ▪ (Temple, Koranyi, & Nahata 2001) USA; (Gibb 2003) Europe ; (Soza-Vento & Fritz 2007)<br>▪ (Boni et al. 2000) Italy<br>▪ (Martin et al. 2007) USA<br>▪ (Van Dyke et al.2002) USA |
| | Adverse drug events | ▪ Adverse drug events, a barrier to adherence<br>▪ Side-effects did not pose a barrier in adherence study | ▪ (Temple, 2001) ; (Goode et al. 2003); (Soza-Vento & Fritz 2007) USA ; (Pugatch et al 2002) USA<br>▪ (Mukhtar-Yola et al. 2006) |

| Domain | Variable | Evidence from Studies | Citation |
|---|---|---|---|
| | | | Nigeria |
| **Caregiver characteristics** | Maternal Health beliefs | ▪ Caregiver beliefs about treatment, a barrier to adherence<br>▪ Stronger motivation based on perceived benefits of ARVs influence adherence | ▪ (Reddington et al. 2000); (Soza-Vento & Fritz 2007)<br>▪ (Hammami et al.2004) |
| | Number of perceived barriers | ▪ Number of perceived barriers to treatment, linked to caregiver beliefs about treatment, a barrier to adherence. | ▪ (Steele et al. 2001); (Marhefka et al. 2004) USA |
| | Relationship to child | ▪ Children receiving drugs from foster parents, more adherent than children receiving from biological parents ($p < 0.05$)<br>▪ Good adherence (95.5%) found in cohort where majority of children had biological parents (16/25) | ▪ Giacomet (2003) Italy ; (Van Dyke et al. 2002) USA<br>▪ (Natu & Daga 2007) India |
| | Caregiver knowledge of treatment | ▪ High caregiver knowledge of Rx significantly associated with undetectable viral load<br>▪ Lack of info or research about effects of HAART, a barrier to adherence<br>▪ Better regimen knowledge associated with better adherence<br>▪ Internalization of medical knowledge regarding HIV and treatment associated with adherence | ▪ (Nicholson et al. 2005) USA<br>▪ (Goode et al. 2003) Australia<br>▪ (Martin 2007) USA<br>▪ (Hammami et al. 2004) |
| | Educational status (literacy) | ▪ No significant association between educational level and adherence<br>▪ Low educational levels consistently linked to non-adherence (A literature review) | ▪ (Martin et al.2007) USA<br>▪ (Fogarty et al. 2002) |
| | HIV status | ▪ Caregiver HIV status impacts | ▪ (Brackis-Cott et al. 2003) |

| Domain | Variable | Evidence from Studies | Citation |
|---|---|---|---|
| | | negatively on child's adherence | |
| | Substance use | ▪ Caregivers with substance abuse problems impact on child's adherence (physician reports) | ▪ (Brackis-Cott et al. 2003) USA |
| | Mental health status | ▪ Psychological factors impact negatively on adherence<br>▪ Higher caregiver stress was strongly associated with non-adherence ($p<0.01$)<br>▪ Parental anxiety associated with adherence. A 7.6% increase in odds of poorer adherence found with increased anxiety.<br>▪ Psychiatric illness an independent risk factor for non-adherence ($p=0.04$) | ▪ (Giacomet, 2003) Italy<br>▪ (Mellins et al. 2000) USA<br>▪ (Garvie, Lensing, & Rai 2007) USA<br>▪ (Patterson et al. 2000) USA |
| **Socio-economic Characteristics** | Social support | ▪ No association between structural social support and adherence but caregiver knowledge and self-efficacy is significantly associated with adherence in the presence of higher social support and social disclosure of HIV status. | ▪ (Martinez et al. 2000) |
| | Disclosure | ▪ Difficulties in taking or remembering drugs related to fear of disclosure<br>▪ Knowledge of child's HIV status by caregiver only, a barrier to adherence (non-disclosure)<br>▪ Less disclosure to others led to non-adherence ($p<0.05$)<br>▪ Recent disclosure increased adherence in children | ▪ (Gibb et al. 2003) Europe (PENTA)<br>▪ (Nabukeera-Barungi et al. 2007) Uganda<br>▪ (Mellins et al. 2000) USA<br>▪ (Garvie, Lensing, & Rai 2007) |
| | Family coping skills | ▪ greater problem solving capacities to overcome practical barriers to | ▪ (Hammami et al. 2004) |

| Domain | Variable | Evidence from Studies | Citation |
|---|---|---|---|
| | | adherence impact positively on adherence<br>▪ care-giving /family factors including worse parent-child communication influenced adherence negatively (p<0.03)<br>▪ complications in day-to-day living impact negatively on adherence (leads to 'forgetting doses') | ▪ (Mellins et al. 2000)<br>▪ (Murphy et al. 2003) USA |
| | Stable housing | ▪ Housing instability associated with non-adherence | ▪ (Belzer et al. 1999) |
| | Income | ▪ Cost of treatment identified as a barrier to adherence | ▪ (Mukhtar-Yola et al. 2006) Nigeria |
| **Health System factors** | Free or payment required services | ▪ Reasons cited for missing doses included running out of medication and not having funds to purchase more | ▪ (Mukhtar-Yola et al. 2006) Nigeria |
| | Patient –provider relationship | ▪ Physician report correlates with viral load (r=-0.39; p<0.05)*hypothesized reason: due to frequent contact and good rapport)<br>▪ Physician report does not correlate with adherence (adherence incorrectly predicted 45% of time) | ▪ (Naar-King et al. 2005) USA<br>▪ (Patterson et al.2000) USA |
| | Travel distance to facility | ▪ Long travel distances to facility (average 72 kms one way), was not found to be a barrier to clinic adherence (95.5% rate for cohort)<br>▪ | ▪ (Natu & Daga 2007) India |

# CHAPTER 3
# STUDY METHODS

## 3.1. Introduction

Chapter 3 outlines the study aims, objectives and methodology. The physical context of the study (site selection, description and personnel) is described together with participant recruitment criteria and procedures. The site description is purposely detailed. It includes a brief history in order to provide a context for the challenges presented to the researcher conducting operational research in a routine clinic without special adaptations considerate of the research being conducted. An overview of the study design, description of the data management and approach to analysis is presented. Finally, the ethical considerations are outlined.

## 3.2. Study Aims and Objectives

The study aim was to characterize paediatric adherence amongst children <7 yrs of age by identifying the measure of adherence most appropriate in a paediatric clinical setting and, identifying factors impacting on their adherence.

### 3.2.1. Specific Objectives

1. To determine the rate of adherence to HAART among children aged 0-6 yrs attending Red Cross Children's War Memorial Children's Hospital's (RXH) infectious diseases outpatient clinic (IDC), using four measures of adherence: namely, (1) medicine measure/pill counts (2) caregiver self-report (3) pharmacy refill (4) clinic attendance.
2. To determine the agreement between the four measures.
3. To determine the agreement of the measures with virological outcome at 6 months since ARV initiation.
4. To identify child, caregiver, Socio-economic and health system factors impacting on adherence to HAART among children in this setting.

5. To make recommendations for the design and implementation of adherence enhancing interventions in this setting.

## 3.3. Site Selection

There are three tertiary level public health paediatric ARV services in the Western Cape Province, namely, Groote Schuur Hospital (Ward G25), Tygerberg Hospital, KIDs Clinical Research Unit (KIDCRU) and RXH. Statistics for 31 March 2004 (prior to commencement of the study), indicate that 78.4% (537/685) of all children treated with HAART in the province were managed at the three aforementioned referral hospitals (HIV/AIDS Directorate. 2004). The ARV treatment provided at this stage (prior to the National ARV roll-out) in all three sites was donor dependent and therefore issued on a relatively limited scale. RXH was chosen as the study site due to the fact that the majority of its patients were already on a provincial sponsored ARV programme and thus more children would have access to treatment thereby impacting positively on potential enrolment numbers. The authorities were approached for permission to conduct the study at the site, which was granted (see Appendix 2).

## 3.4. Study site Description

To allow the reader to understand the service in which the study was conducted and the changes that staff and patients experienced during the period of the study, a brief overview of the history of the clinic will be presented.

***Red Cross War Memorial Children's Hospital (RXH)***

Red Cross War Memorial Children's Hospital (RXH) is one of two tertiary (referral) hospitals in Cape Town associated with the University of Cape Town's Faculty of Health Sciences. However, it is the only hospital on the African continent dedicated exclusively to the care of children (that is, no adults are managed at this hospital). The hospital provides specialist care for children with a wide range of medical and surgical conditions. HIV infection is currently the dominant health problem. Between 40 and 50 % of children who are admitted to the general medical wards are HIV-

infected. Approximately 31% of all deaths and 60% of deaths due to infectious diseases at the hospital are currently related to HIV infection (Grandin et al. 2006).

***Infectious Diseases Outpatient Clinic (IDC) 1990-2003***

The "HIV clinic" is referred to as the Infectious Diseases Outpatient Clinic. This outpatient clinic was started at the hospital in 1990 in response to the growing number of children identified as HIV infected and in need of specialist follow-up. HIV care included regular clinical monitoring including cotrimoxazole prophylaxis, treatment of minor infections, nutritional and micronutrient supplementation, as well as screening for and initiation of treatment for tuberculosis (ongoing TB treatment is provided at primary care level).

In August 2002 a donor driven antiretroviral treatment programme for public sector patients was initiated at the IDC clinic (Eley et al. 2004). Treatment was offered to children and later (in 2003) to their infected caregivers, who met the criteria for initiation of antiretroviral therapy in an effort to provide a 'family centred' approach to the management of HIV infection in children. Since the hospital only received funding for services to children, the IDC clinic entered into collaboration with a non-governmental organization (NGO) Absolute Return for Kids (ARK), to fund the service to the adults. ARK provided the medical doctors to care for the caregivers, pharmacy support and ARV drugs to issue to the caregivers.

The antiretroviral drugs were dispensed through a 'research' pharmacy which was donor funded. This pharmacy operated differently to the normal hospital pharmacy since it served a very small patient base, namely those attending the IDC clinic for ARVs and study participants in clinical trials. There were therefore no long queues and long waiting times at the pharmacy and patients received careful instruction regarding ARV administration. This setting was therefore not typical of routine patient care in the rest of the hospital and in the community. Adherence monitoring was done and feedback given to patients regarding their adherence according to pill counts/medicine measures. Reinforcement of knowledge of the dosing and administration techniques of ARVs was continuously done by the pharmacists.

The IDC clinic provided a comprehensive service including ongoing psychosocial counselling (provided by NGO-appointed lay counsellors), a social work service; home visits for follow-up of defaulters and assessments for treatment initiation; placement in acute respite care when necessary, liaison with community based NGOs for welfare and post hospitalization medical support. Weekly support group meetings are held on clinic days to provide caregivers of HIV infected children to receive information and share experiences thereby gaining support. These groups are facilitated by the lay counsellors.

***IDC 2004 – 2006***

This total reliance on donor funding changed by 2004 with the governments' decision (in November 2003) to provide antiretroviral therapy through the public sector (Department of Health 2003). Between February and November 2004, after the Western Cape province of South Africa began providing HAART to public-sector patients, the donor-funded programme was fully integrated with the provincial programme. By the end of March 2006 the IDC site was one of 37 ARV accredited public sector sites and the largest paediatric ARV service in the Western Cape. The total number of patients receiving HAART in the Province at this time was 16300 of whom 2009 (12.3%) were children (Eley et al. 2006).

There were a series of changes in the way patients in this study were managed at the IDC during the study period. These changes were as results of the shift from a donor-funded service to a service integrated into the normal health services.

From January 2005, all patients established on HAART at the IDC for at least 6 months, were transferred to the main hospital pharmacy as a means of phasing out the ARV dispensing at the research pharmacy, as required by the new system. Two 'ARV' pharmacists, who were integrated in the main hospital pharmacy, were appointed by the Province. This change led to ARV patients sharing the same experience of long queues at the pharmacy as all other patients in the hospital.

In May 2005, there was a policy directive from the Provincial Health Department that all tertiary hospitals should 'decant' their paediatric patients who were stable on HAART to the primary care clinics in their area of residence. A decision was taken to close down the family clinic service in February 2005, and by May 2005, all adults on treatment were transferred to community clinics (in most cases with their children).

This referral resulted in an obligation on the part of paediatricians and IDC staff to mentor clinicians and health care staff at the clinics, in respect of paediatric HIV management and treatment.

It should be noted that this policy was implemented during the recruitment and follow-up phase of the study which resulted in a diminished number of eligible participants for the study as well as the transfer and therefore 'lost to follow-up' of enrolled participants. This had a negative impact on the numbers available for recruitment and for retention of study participants.

Patients transferred out to clinics could not be followed up by the study due to the following reasons: (1) the clinics are governed by different health authorities. Permission to access patients and patient records required formal application from the various authorities. This was not feasible due to the resource constraints on the study and given the time lag for this process and the fact that patients were transferred to various clinics. (2) There were differences in patient record systems available at the clinics compared to the hospital with regard to pharmacy refill records, clinic appointments and laboratory results. These systems were manual and 'study' patients obtained different patient identification numbers which would make it difficult for the researcher to link study participants in the new system. However, we were successful in obtaining the viral load results of five patients who were transferred out to one particular clinic since this clinic was one of the outreach sites to which paediatricians from RXH rendered a mentorship service to strengthen paediatric HIV management at the site.

A further factor to consider was that the IDC at Red Cross Children's Hospital has an active research programme. During this study, there were several ongoing research clinical trials at the facility and some study participants were concurrently enrolled in other trials. This meant that in some instances they were given additional medication such as INH prophylaxis/placebo or micronutrients in another study. These study medications were given in addition to their antiretroviral treatment and added to their 'pill burden' but not counted as part of their adherence assessment in this study. Often enrolment into other studies occurred after enrolment into the adherence study.

The standard of care for children on HAART during the study period included monthly pharmacy refills, clinic visits within 2 weeks to a month of initiation, thereafter monthly clinic visits until the patient is deemed 'stable on HAART', at which point clinic visits may be bi-monthly while pharmacy visits remain monthly. In addition to various blood tests such as tests for anaemia, liver function, immunological (CD4 counts) and virological (HIV DNA Viral load) monitoring is conducted routinely. The data on CD4 counts and viral load collected for this study was part of the routine service and not specifically for the purpose of this study.

The health care team composition fluctuated during the period of the study starting with 1 full-time consultant and 1 clinical nurse practitioner who was working on research trials full-time but assisting on clinic days at the IDC. Several principal medical officers, some of whom later took up positions in the clinic, volunteered their services. Two lay counsellors, employed by and NGO provided interpretation services for IDC doctors, pre and post test counselling, support group facilitation and information to patients regarding HIV and antiretroviral treatment. The number of counsellors increased to five during the period of the study (Table 3.1).

**Table 3.1: Summary of Key changes during study period 2004-2006**

| | Oct-Dec '04 | Jan-March '05 | Apr-June 05 | July-Sept '05 | Oct-Dec '05 | Jan-March '06 | Apr-Nov '06 |
|---|---|---|---|---|---|---|---|
| **Research Stage** | Recruitment /FU | Recruit/ F/U | Recruit/ F/U | Recruit/ F/U | Recruit/ F/U | Follow-up | Follow-up |
| **No. of Children remaining in care** | 329 | 351 | 357 | 471 | 414 | 391 | 288 |
| **New patients starting ART** | 38 | 63 | 66 | 108 | 69 | 61 | 132 |
| **Cumulative Nos. Recruited** | 32 | 56 | 77 | 92 | 97 | 121 | 135 |
| **IDC Staffing** | 2 Research Pharmacists*;<br>3 clinicians<br>1Clinical Nurse Practitioner (p/t);<br>2 counsellors | Additional<br>1 clinician<br>2 Pharmacists (main pharm.);<br>2 nurses**;<br>1 counsellor | Additional<br>2 pharm.assist<br>1 counsellor | Additional<br>1 Social worker | Additional<br>1 data capturer | Additional<br>1 counsellor | No staff changes |
| **Pharmacy change** | Research Pharmacy issue ARVs | Main pharmacy phased in to issue ARVs | Main Pharmacy | Main Pharmacy | Main Pharmacy | Main Pharmacy | Main Pharmacy |
| **Counselling change** | Counsellors pre/post test counselling<br>Drs – HAART initiation | Counsellors pre/post test counselling<br>Drs – HAART initiation | Counsellors pre/post test counselling<br>Drs and counsellors HAART initiation | Counsellors pre/post test counselling<br>Drs and counsellors HAART initiation | Counsellors pre/post test counselling<br>Drs and counsellors HAART initiation | Counsellors pre/post test counselling.<br>Drs and counsellors HAART initiation | Counsellors pre/post test.<br>Drs and counsellors HAART initiation |
| **Clinic Times** | Tues and Fri | Tues and Fri | Tues and Fri | Tuesday, Thursday, Friday | Tuesday, Thursday, Friday | Tuesday, Thursday, Friday | Tuesday, Thursday, Friday |

* The research pharmacists did not provide a service to the IDC paediatric patients from January 2005.

** The nurse previously part-time became full-time

**Abbreviations used in Table 3.1:** F/U= Follow-up; Drs= doctors; Nos.=numbers; Pharm= pharmacy; pharm assist. = pharmacy assistants.

## 3.5. Site Preparation

After Research Ethics approval and permission to conduct the study at RXH was obtained, the study was introduced to the staff of the IDC, where recruitment and follow-up would take place (Appendix 1). A copy of the Standard Operating Procedure (Appendix 5) for the researcher/s was given to the staff which outlined eligibility criteria and recruitment procedures. With permission, a notice informing rotating clinician's in the IDC about the study, was placed on the notice board in the staff tearoom. The researcher was present at every clinic to recruit and inform new staff of the study.

## 3.6. Study Overview

The original plan was to utilize three types of study designs for the adherence study as outlined in Table 3.2. However, because of problems arising from health systems constraints, two of these sub-studies were not pursued, namely, the retrospective study design and the qualitative study design for reasons outlined below.

The implementation of the retrospective study design was abandoned due to the following reasons. A meeting convened by the researcher and colleagues to discuss the study and obtain permission for accessing study sites (two tertiary hospitals and three primary care clinics) on the 21 September 2004, revealed that there had been no standardized system of data collection for children on ARV treatment across sites prior to that date. The time frame for data collection (2002-2004) was prior to the government ARV roll-out programme and thus patients on ARVs were linked to research studies or drugs supplied by private donors. This meant that dispensing records were not consistently available in a format that would have rendered satisfactory results for the review. Moreover, data was not in electronic format and therefore was not easily accessible nor were patients on ARVs easily identifiable from the general hospital system, for selection into the study.

An attempt to conduct a retrospective review at the study site in September 2004 revealed similar problems. While there was adequate data available for patients on

certain trials (not necessarily recorded in patient folders but with study pharmacist), patients receiving ARVs from donations or via their medical aid accounts did not have detailed records with regard to pharmacy issue and collection of ARVs recorded in patient folders. This meant that there were going to be large gaps in the information available and high levels of missing data for key variables. For example, in September 2004, there were approximately 280 patients on treatment at the IDC, however, up-to-date and complete pharmacy ARV dispensing records together with medicine return data was only available for approximately 120 patients. This cohort was part of a research study which was conducted at the time.

The decision was therefore made not to pursue this retrospective method of assessing adherence. The retrospective nature of the data collection would have made it impossible to get meaningful data because of lack of standardized data and lack of consistent data to measure adherence across sites.

No further reference will therefore be made in this report to the retrospective study.

Two qualitative approaches were planned namely: (1) focus group discussions with caregivers of children on HAART (biological vs. non-biological caregivers) and (2) focus group discussions with Health Care workers in the IDC.

One focus group discussion was conducted with a group of nine HIV infected caregivers in March 2005. However, the group was reluctant to focus on the research issue and wanted a space to talk about their feelings regarding the transfer out of patients from the IDC to the primary care clinics, a shift in policy that took place in May 2005. As a result, this discussion was not considered useful in achieving the aims of the focus group discussion. In addition, several non-biological caregivers approached for participation in a separate focus group discussion refused; thus, it was decided to abandon this approach. Similarly, staff turnover at the IDC was continuous due to rotation of doctors and only two staff members remained constant. In addition, the researcher worked closely with the team and it was decided that this may bias the

response of the Health care workers, and the planned approach[24] was thus considered unfeasible. Thus, no further reference will be made to the qualitative studies. The reported research therefore involves a single prospective study incorporating cross-sectional data collection at baseline and prospective data collected at three time points over the period of 6 months.



[24] In-depth interviews with Health Care providers involved in antiretroviral treatment of paediatric patients in the clinic to determine their beliefs and perceptions of patient adherence support needs

**Table 3.2: Overview of Study Designs**

| | Retrospective Study Design | **Prospective Study Design** | Qualitative Study Design |
|---|---|---|---|
| Study Population | Children under 6 yrs on HAART | Caregivers and their Children who commence HAART. | Participants in Prospective Study and Health Care Workers (HCWs) at the Infectious Diseases Clinic |
| Study Site | Three Paediatric HIV clinics in Metropole | Red Cross Children's Hospital | Red Cross Children's Hospital |
| Number enrolled | 300 | 135 | 12-20 Caregivers<br>10 Health Care Workers |
| AIM | To determine the rate of adherence in children during the period 1 January 2002 to 31 December 2002. | 1)To determine the rate of adherence to HAART among children aged 0-6 yrs attending Red Cross Children's War Memorial Children's Hospital's (RXH) infectious diseases outpatient clinic (IDC), using four measures of adherence: namely, (1) medicine measure/pill counts (2) caregiver self-report (3) pharmacy refill (4) clinic attendance.<br>2) To determine the correlation between the four measures.<br>3) To determine the correlation of the measures with virological outcome at 6 months since ARV initiation.<br>4) To identify child, caregiver, Socio-economic and health system factors impacting on adherence to HAART among children in this setting.<br>5) To make recommendations for the design and implementation of adherence enhancing interventions in this setting. | To determine caregivers and health care workers perceptions of adherence support needs and to identify institutional, policy and staff barriers as well as enabling factors, to patient adherence. |
| Data Collection Method | A record review of all cases identified at each facility as having commenced treatment during the period 1 Jan-31 Dec..2002.<br>Extract pharmacy refill data from existing data bases, patient folders and pharmacy records at three institutions to enter onto case report form. | Recruitment & enrolment of new patients on HAART between the periods, 1 October 2004 – 31 November 2005.<br>Administered structured "baseline questionnaires" to all participants within one month after commencing treatment.<br><br>Administer self-adherence questionnaire at M1,3,6; collect monthly data from pharmacy on CRF (prescription refills over period of 6 months), conduct meds/pill counts) at M1,3,6<br>Capture monthly appointment schedules over 6 months.<br>Capture CD4 and viral load results from lab reports at baseline | Two Focus groups will be held with caregivers (biological parents and other).<br><br>In-depth interviews will be held with the various categories of HCWs (doctors, nurses, counsellors, social workers, pharmacists) |

| | Retrospective Study Design | **Prospective Study Design** | Qualitative Study Design |
|---|---|---|---|
| | | and 6 months.<br>Capture data on changes in height and weight, hospitalizations and changes in household circumstances. | A HCW team self-assessment will be facilitated by the PI. This will be in the form of a team workshop. Key members of the team will be identified before hand and encouraged to participate. |
| Primary Analysis | Sub-study Not undertaken | Descriptive statistics for basic characterization of cohort. Crude bivariate comparisons (using Student's T-Test and ANOVA to compare means. Fisher's Exact tests and Yates' corrected chi-square to compare proportions to identify basic unadjusted associations.<br>A series of chi-square tests conducted to determine a relationship between the categorical predictors/controls to avoid multi-co linearity in the regression models. Kruskal Wallis tests were used to examine logged base viral load with various controls. Sensitivity and specificity tests were conducted to determine cut-off points for adherence. Box-plots and Spearman's correlation were used to examine correlation between adherence measures and between adherence measures and viral load. | Sub-study not undertaken |

## 3.7. Prospective cohort design

A prospective cohort study design was used involving 135 children, who were enrolled between 1 October 2004 and 9 June 2006. They were followed up for 6 months. The last follow-up assessment was conducted in November 2006.

### 3.7.1. Study Population and Sample

Primary caregivers and paediatric patient pairs, who commenced HAART treatment between 1 October 2004 and 31 June 2006, at Red Cross Children's Hospital's Infectious Diseases outpatient clinic, were enrolled into the study.

***Definition of primary caregiver:** The person, with whom the child lives for ≥ five days of the week and is responsible for the welfare of the child. This includes grandmothers, aunts, uncles, foster parents as well as biological parents.

*Inclusion Criteria*

- Primary caregivers of children, younger than seven years of age at time of initiation of treatment, accompanying the child to hospital visits.
- Children who are treatment naïve and commencing treatment on the day of enrolment or within one month prior to enrolment.

*Exclusion Criteria*

- Any child living in an institutional setting or children's home for long term care; or those waiting to go to foster homes, at the initiation of ARV treatment.
- Children on treatment for more than 1 month prior to enrolment.

The reason for the exclusion of institutionalized children was based on the experience that most of these children are usually accompanied to hospital by various caregivers. These are often volunteers who are not involved in the daily administration of medication and often do not have a history for the child. They often accompany more than one child at a time. Children in institutions usually receive their medications, regularly and on time since this is part of the routine care provided. The utility of

adherence data for this group of paediatric patients is limited when considering the large numbers of patients in routine ambulatory non-institutional care.

Children on treatment longer than 1 month were excluded for a two main reasons. First, because factors such as, knowing the names of drugs; knowledge of treatment; perception of side effect profiles of children; difficulty with administration of medicine and the perception of child health status at initiation, would be different for caregivers whose children were on treatment longer, compared to those whose children are just starting out treatment. Second, several variables were used to contrast baseline characteristics (at initiation of treatment) with outcomes at 6 months. These variables would not be clearly defined with the inclusion of children starting at varying times before enrolment into the study.

### 3.7.2. Measures of adherence

***Caregiver Self-report:***

Adherence was measured using the Paediatric AIDS Clinical Trials Group (PACTG) adherence questionnaire which is based on 3-day recall of missed doses preceding the clinic visit, as well as the correct identification / description of prescribed medication (Appendix 13). This information was obtained at months 1, 3 and 6.

*Cumulative Adherence Formula for caregiver self-report:*

Cumulative Adherence was calculated as: sum (number of doses taken yesterday)+ (number of doses taken 2 days ago) + (number of doses taken 3 days ago) /sum (total number of doses) for each Month. This was averaged (that is, divided by the total number of months for which there was a measure) and expressed as a percent.

In addition, mean adherence rates were calculated for each ARV, averaged over the follow-up period. Cumulative frequency of missed doses per ARV was calculated from caregiver self-report measures.

***Pharmacy refills:***

This information was abstracted monthly from the pharmacy chart in the patient folder. Adherence was calculated by computing the percentage 'on time' medication collections over the total amount required over a specific period. 'On time' collections were defined as 4 days around the given date but no longer than 2 days after the given date.

*Adherence Formula for Pharmacy refill:*

The number of 'on-time' collections completed/expected number of collections for the study period multiplied by 100

***Clinic attendance:***

This information was abstracted from the patient folder and IDC ARV Case report form (Appendix 6). Adherence was calculated as the percentage 'on time' scheduled clinic appointments kept/the total number of scheduled visits within a specified period of time. On-time attendance was defined as 'scheduled appointment kept'.

*Adherence Formula for Clinic visit:*

The number of 'on-time' visits completed / expected number of appointments for the period multiplied by 100.

***Cumulative Adherence Measure***

A cumulative adherence measure was calculated as follows: sum (adherence (%) Month 1 + adherence (%) Month 3 + adherence month 6)/ 3; where data was missing for any particular time point, the data was divided by the remaining data, for example, adherence Month 1 + adherence Month 3 / 2.

***Pill /medicine Counts:***

The researcher conducted the pill counts in a separate room, while the research assistant interviewed the caregiver at visits 1, 3 and 6 months. Adherence was calculated as a percentage by computing the difference between remaining medication and issued medication/expected doses. Remaining liquid formulations were measured, using a measuring beaker.

*Adherence formula for Medicine Measure:*

Total amount of medicine issued (expressed as millilitres in liquid form or number of capsules in capsule form) - amount of returned medicine (mls)/capsules / total expected dosing for preceding period of 1 month (mls/capsules) multiplied by 100. This was done separately for each ARV in the regimen, namely, three ARVs per child.

[Note: An amount of medication carried over from previous month was added to the amount issued in subsequent month]. This was usually noted by the pharmacist to keep over prescription to a minimum.

***Virological and Immunological markers***

Viral loads and CD4 absolute counts as well as CD4 percentages, were abstracted from hospital records at baseline (date closest to initiation of ART) and at 6 months. Bloods are taken routinely (baseline and 6 months, thereafter annually) by IDC clinic staff. The bloods are sent to the virology laboratory situated at Groote Schuur Hospital for testing. Results are posted electronically via the laboratory database to which the hospital has access.



### 3.7.3. Sample Size Determination

Due to the paucity of data regarding paediatric adherence to antiretroviral treatment in resource-limited settings, effect sizes were determined from literature from the developed world. As outline in chapter 2, adherence to medical advice in general varies widely and in paediatric populations average approximately 50% (Fotheringham & Sawyer 1995). However, studies in paediatric HIV have shown the size of the difference between adherent and non-adherent groups ranged from 0% to 40% when measuring adherence by caregiver self-report (Steele & Grauer 2003); (Reddington et al. 2000), to approximately 60% when measuring adherence by clinic appointments and knowledge of regimens (Katko et.al. 2001).

The above data has wide variability and the sample size for the present study was therefore based on 'Cohen's rule of thumb'[25] for a medium effect of 0.50 to determine differences between groups (Table 3.3). Using G*Power statistical software, the Table 3.3 was generated. For 80% power with Alpha ($\propto$ ) set at .05, the required sample size is 128. This study recruited 135 participants. It was hypothesized that a sample size of 135 would provide sufficient power to identify predictors for adherence or non-adherence that are in the order of odds ratios of 0.50 or conversely odds ratios of 2.0.

For a sample size based on an effect size of 0.20 (small effect) with 80% power with Alpha at 0.05, the number of participants needed to be at least 788. This number was prohibitive in terms of the amount of time it would have needed to recruit this size from one site (Appendix 9). In addition, the lack of funding for the study made this target unfeasible.



**Table 3.3: Power and Sample size calculation**

| Effect size | Alpha | Power | Sample size | Actual Power |
|---|---|---|---|---|
| 0.50 | 0.05 | .80 | 128 | 0.8015 |
| 0.50 | 0.05 | .70 | 102 | 0.7056 |
| 0.20 | 0.05 | .80 | 788 | 0.8017 |

### 3.7.4. Research Personnel

The researcher utilized the services of a research assistant. There were two different assistants for the duration of the study. The first one was a social science graduate enrolled in the MPH programme. The research assistant had experience in conducting interviews for surveys. He was trained in the use of the research instruments used in the study.

In June 2005, the research assistant resigned from the university and a lay counsellor, based at the RXH, was recruited in the research assistant position. She was an

[25] (Cohen et al. 2003)

experienced counsellor who was working at the hospital for approximately three years at the time of recruitment to the study. She was trained by the researcher and mentored by the previous incumbent before he left. There were only two interviewers (not concurrently), there was therefore limited scope for inter-interviewer variability.[26]

All interviews were conducted in Xhosa or English (as required); no participants wanted to speak Afrikaans. The researcher conducted all medicine measures/pill counts. A document detailing the standard operating procedures was developed as a guide for the research assistant who was responsible for assisting the researcher with recruitment, enrolment and interviewing of patients (Appendix 5).

### 3.7.5. Study Implementation

In the following section, the recruitment, selection, enrolment and follow-up procedures will be explained. Thereafter, a detailed explanation of each instrument used in the study will be provided.

#### 3.7.5.1. Interviews

All interviews were conducted in private in a separate room in the first language of the caregiver within the area in which the IDC clinic was operating.[27] These interviews were conducted during the routine clinic visits to the hospital, while the participant was waiting to see the doctor or after they had seen the doctor. They were allowed to interrupt the interviewing process to see the doctor if their names were called during the interview so that the normal flow of the clinic was not interrupted. The recruitment interviews at 1, 3 and 6 months, lasted approximately 30-45 minutes while the follow-up interviews took approximately 15-20 minutes. Four data collection points were therefore available for analysis.

[26] This was not measured.

[27] Note that the IDC does not have a dedicated space within the hospital from which it operates. The clinic shares the rooms of other outpatient clinics and therefore operates from different clinics on different days.

### 3.7.5.2. Recruitment and selection Procedure

Caregivers of children on ARVs were recruited from two sources in the hospital, namely, the outpatient IDC clinic or the in-patient wards. The patients initiated on treatment in the wards were identified by the researcher on the Monday ward round where candidates for ARV initiation were brought to the attention of the IDC consultants by the ward medical personnel. The researcher was invited to join the clinical team on these rounds for the purpose of recruitment. In addition, patients were either referred to the study by the doctors at the outpatient clinic or identified by the researcher via the outpatient clinic register.

The routine schedule for outpatients commencing ARV is to allow at least two visits to the counsellor and nurse for ARV treatment literacy training before actual medicines were dispensed. However, patients referred from the wards were usually started on treatment in the wards and then referred for follow-up visits to the outpatient clinic after discharge.



### 3.6.7.3. Enrolment Procedure

The primary caregivers of eligible patients were approached and informed about the study and if he/she agreed to participate in the study, signed consent for participation in the study was obtained (Appendix 3). A copy of the consent form was given to the participant and a copy kept in the study files. The forms were in English and Xhosa and the caregiver was given a choice regarding whether they wanted to have a copy of the consent form in English or Xhosa. The consent process was conducted in the participant's preferred language. Enrolment procedures were completed at this visit (Table 3 2). The majority of the patients attending the IDC are Xhosa speaking and all interviews were conducted either in Xhosa or in English. No other languages such as Afrikaans were necessary.

The following instruments were administered to the caregiver on enrolment:

- An enrolment form which included contact information, current health complaints and history regarding access to the IDC clinic, which was

solicited from the caregiver and medical history, which was abstracted from the patient folder.

- The Baseline questionnaire: Children who were only starting treatment on the day of enrolment, stopped at question H, which related to medication administration practice (if the child had commenced treatment on the day of enrolment).[28]
- The Centre for Epidemiologic Studies Depression Scale (CES-D) (Appendix 11).
- Medical Outcome Study Social Support Survey – Revised (MOSSSS) (Appendix 12).

The following procedures were completed by the researcher/assistant subsequent to the enrolment visit.

- Completion of the medical enrolment form by abstracting information from the patient folder or hospital database (for CD4 and viral load results).[29]
- A review of the patient folder for information related to baseline clinical condition and latest hospitalization prior to commencing HAART was conducted by the researcher.
- The next appointment date (verified with clerk if not obtained from caregiver during the interview).



### 3.6.7.4. Follow-up procedure (Months 1, 3, 6)

The research assistant interviewed the patient and completed the prospective case report form, which captured any changes in circumstances and monitored growth and health outcomes. The depression screening tool (CES-D) and the perceived social

[28] *Socio-demographic and treatment Baseline Data Collection* (completed within 4-6 weeks after initiation on HAART). This questionnaire was completed in two parts if (1) there were time constraints for the patient or (2) the questionnaire was administered on the day of ARV initiation. At enrolment parts A to G were completed. At 2wks adherence check visit or 1 month (whichever appointment was given by the doctors), the questionnaire was completed (parts H-I).

[29] A nurse was approached to obtain the information from the hospital database due to the 'limited access to medical records' policy of the hospital

support measure (MOSSSS) was administered at each interval, as well as the caregiver self-reported adherence questionnaire.

While the patient was being interviewed by the research assistant, the returned medicine bottles were obtained by the researcher. The contents were measured and recorded on the "Medication follow-up assessment form" (Appendix 7).

The following procedures were completed by the researcher subsequent to the study visit.

1. The patient's appointment visit date was captured in the clinic visit record database and it was determined whether the patient's appointment visit was on time or not, according to the previous clinic appointment date (TCA[30]) date recorded.

   Note: An 'on-time appointment was defined as 'on time' 4 days around the given date but no longer than 2 days after the given date).
2. Medicine issue amounts and refill dates were obtained from pharmacy charts (where information was not recorded on the chart, the pharmacy was contacted to obtain the information from the pharmacy database).
3. Clinic return appointment date obtained (from either patient or clerk).

Table 3.4 below provides a summary of the study procedures.



[30] 'TCA' stands for "to come again', referring to the follow-up clinic appointment date for the patient.

**Table 3.4: Study Procedure Outline**

| | Baseline | Month 1 | Month 3 | Month 6 |
|---|---|---|---|---|
| **Enrolment** | √ | | | |
| **Socio-demographic questionnaire** | √ **(Till question 'H')** | √ **(from question 'I')** | | |
| **Case Report Form*** | | √ | √ | √ |
| **CES-D (caregiver)** | √ | √ | √ | √ |
| **MOSSS (caregiver)** | √ | √ | √ | √ |
| **Caregiver Self-reported adherence** | | √ | √ | √ |
| **Med measure/pill counts** | | √ | √ | √ |
| **CD4 counts & CD4%** | √ | | | √ |
| **Viral Load** | √ | | | √ |

| **Months** | **1** | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|---|
| **Pharmacy Refill** | √ | √ | √ | √ | √ | √ |
| **Clinic attendance** | √ | √ | √ | √ | √ | √ |

***** Form capturing any changes in circumstances including growth monitoring.

**Note:** Pharmacy refill data and clinic attendance were captured from hospital records on a monthly basis.

### 3.7.5.5. Study Instruments

***Consent Forms***

The consent form outlined the aim of the study and the approximate duration of the interviews. Permission to access the child's patient folder for medical and virological data was requested. The caregiver was informed of the possibility of being recruited into a focus group discussion and requested to indicate their willingness to participate in any future focus groups.[31] Finally, they were informed of their right to refuse participation and should they agree to participate initially, they could withdraw at any

[31] It was envisaged that two focus groups would be convened viz. one with biological parents and one with non-biological parents to explore issues which may emerged from the data indicating differences in factors between these two groups. It was hypothesized that there would be differences. However, the majority of caregivers were found to be biological parents. There was therefore no basis for conducting the separate focus groups.

stage without prejudice to the child's medical care. The consent form was administered in the patient's first language and they were given a copy to take home.

***Enrolment Forms (Appendix 4)***

These were in two parts. Part 1 consisted of information provided by the caregiver such as caregiver and child demographic details; ARV start date; history of clinic attendance at the IDC and referral route; the caregiver's opinion of the child's health condition prior to commencement of HAART; and child's ARV regimen. Information about the caregiver's perception of the reason for initiation of ARV and source of this information was solicited.

In part 2, the medical information obtained from the patient folders was documented. This included the verification of the date of commencement of IDC clinic attendance, route of referral and HAART regimen. Other information such as TB status at enrolment, PMTCT participation by mother, details of last hospitalization (prior to enrolment), medical reason for initiation of HAART, significant medical problems, clinical staging, other drugs prescribed, baseline weight, height, CD4 and viral load data.



***Baseline Questionnaire (Appendix 10)***

The design of this instrument was based on the literature regarding adherence which was predominantly related to adult populations since at the planning and initiation of this research, there was a paucity of data for the paediatric population. It was also hypothesis driven based on the evidence from the literature.[32] Data was captured on this form at one point in time only.

This questionnaire collected data across the following domains: (1) Child characteristics which included child-minding arrangements and other health and demographic factors. (2) Caregiver characteristics (primary caregiver status**,** that is**,** relationship to child), demographic details: *caregiver details* such as age, educational, marital, and employment status; source of financial support; caregiver HIV status,

[32] Reference to the hypotheses underlying the variables are provided in Appendix 8.

health status, history of compliance to TB treatment or ARVs, if applicable, fertility plans (applicable to biological mothers). (3) Socio-economic characteristics such as type of housing, access to water and sanitation, HIV infection among household members; HIV treatment among other members of household excluding index child; Issues of disclosure, stigma and discrimination indicated by questions such as who knows the child's status, does the child know his/her status (not applicable in the case of children younger than 3 years) were explored. Caregiver perceptions of when the 'right time' for disclosure to the child was and who the best person for initiation of the process of disclosure was and solicitation of bad experiences related to disclosure of HIV status; (7)With regard to social support, the following information was elicited**:** support group attendance by caregiver and perception of household, friends and family support. One section dealt with how ARVs fit into the daily routine, who the responsible person for administration of the morning and evening doses were and the type of reminder tools used. Specific information was obtained regarding the weekend routine; the ease of administration for each ARV and utensils used for administration (e.g. syringes, cups, spoons etc); means of coping when the child refused medicine. This information was obtained after the child had been on ARVs for at least 2 weeks. Caregiver knowledge, attitude and practice regarding HIV and Treatment including the practice of consulting traditional healers were probed. An open-ended section for general comments about ARVs or the child provided the caregiver with an opportunity to inform the interviewer of any additional information.

***Prospective Case Report Form (Appendix 6)***

The data were captured on this form at every follow-up visit. The following data were captured: HAART Regimen (to allow for any changes), height and weight, TB treatment status, co-trimoxazole prescription[33], co-administration of any other medication and the reasons, history of hospitalization since the last visit, caregiver complaints about the child's health, possible side-effects, appetite and household food security, changes in household routine or child-minding arrangements, since the last visit and any significant family events since last visit (e.g. funerals, hospitalizations of

[33] Co-trimoxazole was usually stopped once patients were established on HAART – hence this was monitored.

other family/household members, illness of siblings/caregiver, retrenchments, house moves).

***The Centre for Epidemiologic Studies Depression Scale (CES-D)***

This instrument was administered to caregivers at baseline and at each subsequent follow-up visit (Months 1, 3 and 6).

***Description (see Appendix 11)***

The CES-D is one of the most widely used self-report depression screening instruments and has been translated into several different languages and administered to a wide range of populations. In this study it was translated into Xhosa[34] (see section on Translations). It is commonly used in primary care practice (Schulberg et al. 1985). Brandt (2007) found that thirteen of the studies reviewed on the psychological adjustment of HIV-infected women, employed the CES-D, including three longitudinal studies (Milan et al. 2005; Miles, Gillespie, & Holditch-Davis 2001; Richardson et al. 2001) and two conducted in developing country settings (Thailand and Uganda) by (Bennetts et al. 1999; Kaharuza et al. 2006). In South Africa, two studies with HIV-infected populations have used the CES-D. Forsyth et al (2005) conducted research with poor, HIV-infected pregnant women in Pretoria, while Brandt (2007) employed the CES-D to assess the mental health of poor HIV infected women as caregivers of children in Cape Town

The CES-D is a self-report instrument developed to measure current levels of depressive symptoms in the general population, and as a first-stage screening device (as opposed to diagnostic) in clinical and research settings (Radloff 1977). The 20-item checklist requires the person to rate the presence and frequency of symptoms experienced for the 'past week' on a four-point scale ranging from "rarely or none of the time" (0) to "most or all of the time" (3) – that is 0,1,2,3 options. Total scores range from 0 to 60, with higher scores indicating higher levels of depressive symptoms.

[34] The English was translated into Xhosa by one person and back translated into English by another. The research also corroborated the translation with Brandt(2007) who had conducted a concurrent independent translation. The same translated instrument was used in research by Brandt and myself.

*Psychometric properties*

In the original study involving this instrument, a score of 16 was used as an arbitrary cut-off to compare the proportion of individuals in the general and clinical populations who scored at or above this point (21% and 70% respectively (Radloff 1977). According to Radloff the instrument demonstrated high internal consistency among both the general population ($\propto$ = .85) and the psychiatric population ($\propto$=.90). This finding has been verified by subsequent studies(Hann, Winter, & Jacobsen 1989; Lewinsohn et al. 1997; Measurement Excellence and Training Resource Information Center 2002; Myers & Weissman 1980)

In her analysis, Brandt (2007) used a cut-off of 10 in addition to controlling for 5 items in the scale indicating somatic symptoms (items 2, 5, 7, 11 and 20 (i.e. restless sleep, poor appetite, fatigue, lack of energy and poor concentration). The criteria to determine an appropriate cut-off for the reduced scale was that suggested by (Radloff & Locke 1986), namely, "the cut-off is that score that identifies the upper 20% of the distribution". Several studies do not employ a revised cut-off score when excluding somatic items (Milan et al. 2005 ; Simoni & Ng 2000).

Another method used by some researchers is to weight the scores in order to retain the range of the original CES-D from 0 to 60 as well as the typical cut-off score (Schrimshaw 2003). The use of this cut-off by Schrimshaw did not change the results significantly. The prevalence of depressive symptoms remained high within the HIV infected group in both instances compared to the HIV negative group of women. [35]

Validity of the instrument in resource-poor settings was established by Kaharuza et al (2006) in their study with HIV-infected adults in Uganda where they report construct validity of the CES-D was adequate. In Brandt's (2007)study good internal consistency was found with a Cronbach's alpha of 0 .79.

***Medical Outcome Study Social Support Survey – Revised (MOSSSS)***

This instrument was administered to the caregivers at baseline and each subsequent visit (Months 1, 3 and 6).

[35] I acknowledge Rene Brandt for sharing this information with me.

*Description (see Appendix 12)*

In its original form, the Medical Outcome Study Social Support Survey (MOSSSS) is a 19-item scale developed to assess various dimensions of functional social support received by persons with chronic conditions. In addition to a question that elicits information regarding network size, respondents rate how frequently they perceive tangible support, affectionate support, positive social interaction and emotional/informational support to be available when they need it on a 5-point Likert scale. Responses ranged from 1 ("None of the time") to 5 ("All of the time"), with higher scores indicating that support is more frequently available. This scale was first used to measure the social support of HIV-infected women (Sherbourne & Stewart 1991).

For the purpose of this study the adaptation by (Brandt 2007) who also conducted her study in Cape Town, was used. She had modified it in two ways, firstly, by the addition of an item regarding assistance with care giving responsibilities ("Someone to help you take care of your children when you can't") in order to tap support related to child care. Secondly, questions pertaining to satisfaction with the four types of social support assessed by the scale were included. The formulation of these questions was taken from the Social Support Questionnaire (Sarason et al. 1983). Respondents were asked to indicate their degree of satisfaction with a dichotomous choice of a smiling or an unhappy face.[36] A flash card depicting the ratings and faces was made for the participant's ease of reference during the interview. The rationale for this adaptation as reported by Brandt, is that in addition to perceived support, satisfaction with support was hypothesized to be more predictive of women's physical and psychological wellbeing than network size and received support (Brandt 2007).

*Psychometric properties*

Data for the development and validation of the MOSSSS was drawn from a sample of 2 987 patients who participated in a larger study of health care systems in the US (Sherbourne & Stewart 1991). Based on this sample of ambulatory general medical

[36] Since Brandt and I were working with similar populations, we felt that utilizing the same instruments for our separate studies, would add to the scientific body of knowledge in a manner which is comparable.

patients, mean scores for total support, as well as tangible support, positive social interaction and emotional-informational support were 70 (out of 100), with affectionate support scoring slightly higher at 74. Results also confirmed that the MOS had good internal consistency (Cronbach alphas = .91-.97) and one-year test-retest reliability (stability coefficients = .72-.78) (ibid).

Brandt (2007) confirmed these reliability results. Results from her study established that total scores and subscale scores had adequate reliability. Cronbach's alphas for total support and total satisfaction scores ranged from .83-.92, while subscale scores for availability of support ranged from .75-.86 and for satisfaction with support from .54-.81. Only satisfaction with affectionate support scored below .65, indicating moderate internal consistency.

### 3.7.5.6. Translation of Instruments

All questionnaires, tools and consent forms were translated into Xhosa by the first research assistant (graduate). The back translation was conducted by an independent translator for verification. The translated documents were tested among six Xhosa-speaking lay counsellors for verification of meaning and vernacular and revised. For consistency of meaning and interpretation, both the English and Xhosa versions were printed on the questionnaires.

## 3.8. Data Capture and Analysis

The research questions outlined in Table 4 were developed to guide the analysis of the data.

**Table 3.5: Research Questions**

**Objective 1:**

1. What is the mean rate of adherence at 1, 3 & 6 months for each ARV amongst the cohort using the Medicine measure?
2. What is the mean rate of adherence at 1, 3 &6 months as measured by self-report method?
3. What is the mean rate of adherence at 1, 3 & 6 months as measured by on-time pharmacy collection?
4. What is the mean rate of adherence at 1, 3 &6 months as measured by on-time clinic attendance?
5. What are the mean adherence rates for the follow-up period (6 months)?

**Objectives 2 & 3:**

1. What is the agreement between the four adherence measures and viral load at 6 months after treatment initiation?
2. How do each of the measures compare with each other?
3. Which is the 'best' method for measuring adherence in this study?

**Objective 4:**

1. Which child, caregiver, health and socio-economic characteristics impact on adherence to HAART?
2. What is the prevalence of depression symptoms amongst caregivers?
3. What is the level of perceived social support and satisfaction amongst caregivers?
4. Does caregiver psychological factors such as depression and perceived social support impact on adherence?

A database was designed using the Microsoft™ Access programme. Raw data was captured from the questionnaires into Access©. All capturing was completed by the researcher. The database was exported to STATA™ for Windows version 9 for data cleaning and analysis. A subset of 10% of the source documents was randomly chosen for verification of captured data to ensure quality control. Verification of data was done manually by checking study data capture form in conjunction with patient folders and IDC CRFs to verify clinical outcomes and socio-demographic data. In addition, each record of the total cohort was checked manually according to the criteria on the 'quality control sheet' at the end of the recruitment and follow-up period. Source documents included abstracted data on case report forms, questionnaires. In the case of missing laboratory results, these were obtained from the hospital's computerized records.

While cleaning data the researcher created variables not in the original data base in a format suitable for analysis. This applied particularly to the variable names for the various measures of adherence. Formal statistical analysis was preceded by appropriate exploratory analysis, both descriptive and bivariate. Descriptive analysis included computing means, standard deviations and measures of skewness for continuous variables, and generating frequency distributions for categorical variables. Bivariate analysis included correlational analyses and Chi-squared tests.

The main analysis was divided into three parts, namely: Part 1, described in Chapter 4; Part 2, described in chapter 5 and Part 3, described in Chapter 6.



### 3.8.1. Part 1: Characterization of cohort and adherence rates

Descriptive statistics were employed for basic characterization of the cohort. Adherence rates were determined for each measure of adherence in the following manner:

***Caregiver self-report**:*

Data collected at month 1, month 3 and month 6 using the Paediatric AIDS Clinical Trials Group (PACTG) International Adherence Questionnaire (Appendix 13), was

averaged to a cumulative adherence rate using a simple average. All observations with available data were included, that is, if a child, was transferred, died or defaulted during follow-up all data was included till the time of attrition and averaged.

***Cumulative Adherence Formula for caregiver self-report****:*

Cumulative Adherence was calculated as sum (yesterday+2 days +3 days)/sum (doses) for Month 1+Month 2+ Month 3/3, expressed as a percent.

In addition, mean adherence rates were calculated for each ARV, averaged over the follow-up period. Cumulative frequency of missed doses per ARV was calculated from caregiver self-report measures.

***Medicine Measure***

Data from monthly pharmacy collections were abstracted from patient medication charts or the pharmacy computer in the case of incomplete or missing data on the charts for amounts of syrup or capsules issued for each ARV, as well as dosing information. This was noted on the medication follow-up assessment form (Appendix 7) from which the return medication was deducted.

*Adherence formula for Medicine Measure:*

Total amount of medicine issued (mls) / capsules – amount of returned meds (mls)/capsules/ total expected dosing for preceding period of 1 month (mls/capsules) x 100.

[Note: An amount of medication carried over from previous month was added to the amount issued in subsequent month]. This was usually noted by the pharmacist to keep over prescription to a minimum.

***Pharmacy refill:***

Data on pharmacy refill dates and return dates were abstracted from the patient medication chart. These were subsequently evaluated for 'on-time' collection. 'On-time' collection was defined as no more than 4 days around the appointment date but no longer than 2 days beyond the appointment date.

*Adherence Formula for Pharmacy refill:*

The number of 'on-time' collections divided by expected number of collections, multiplied by 100

***Clinic Visits***

Data on clinic attendance and appointment dates were abstracted from the patient folder and clinic register (where appointment dates were not noted in the folder). These were subsequently evaluated for 'on-time' visits. 'On-time' visits were defined as no more than 4 days around the appointment date but no longer than 2 days beyond the appointment date. This evaluation was conducted by programming the database to calculate (appointment date- visit date). Where patients had called in to change the appointment date before hand, the new date was captured as the appointment date with notation to that effect. This only occurred in one instance.

*Adherence Formula for Clinic visit:*

The number of 'on-time' visits divided by expected number of appointments, multiplied by 100.

### 3.8.2. Part 2: Adherence Measures

Estimation of agreement between measures explored the following research questions:

***(1) Do the four measures of adherence agree with each other?***

Data was skewed thus Spearman's correlation matrix was employed to determine agreement between measures because the assumption of normality was violated.

***(2) How does each measure agree with 6-month viral load?***

In the absence of a 'gold standard' measure of adherence, viral load was chosen as the reference measure for adherence. The reason for this choice is two-fold: (1) the data were available routinely, and (2) virological suppression is the desired outcome to determine treatment success. This is possible in a treatment naïve population such as the participants of the present study. Electronic measuring devices have been used as a 'gold standard' but the cost is prohibitive and found to be impractical, especially for

prospective studies with follow-up periods > 3 months, in the monitoring of syrups (Muller et al. 2007).

The data for viral load at 6 months was skewed and was log transformed to the base 10 (a 1 unit increase corresponds to a ten-fold increase in the response) which resulted in a normal distribution.

Firstly, control variables were identified which were hypothesized to influence viral load at 6 months using box plots and Kruskal Wallis tests.

Secondly, unadjusted and correlation analyses adjusted for disease severity were employed to determine the agreement between adherence measures and viral load at 6 months.

Thirdly, multivariate models were conducted to identify the strength of agreement of each measure with viral load in the presence of disease severity variables.

*(3)* ***What is the best cut-off threshold for adherence?***

Using undetectable viral load (<400 copies per ml) as the reference measure, sensitivity and specificity analysis with Receiver Operator Curves (ROC) were conducted for each measure. To further increase specificity values, analyses using a composite measure of adherence were conducted. First, three measures were combined into a composite measure by averaging the three adherence scores; then two measures were combined in the same way. The cut-off with the highest predictive value (correct classification) as well as most 'evenly balanced' sensitivity and specificity values was deemed to indicate the best cut-off threshold for the creation of a dichotomous adherence variable.

### 3.8.3. Part 3: Factors influencing adherence

Part 3 describes the factors associated with adherence. The variables are arranged into four domains. An explanation of the variables is provided in Table 3.6 below:

**Table 3.6: Definitions of variables used in analyses to identify factors associated with adherence.**

.

| Domain | Variable | Definition of variable |
|---|---|---|
| **Child Characteristics** | Age (months) | Child age expressed in months |
| | Gender (M) | Male child |
| | Recent illness | Illness within one month prior to ARV initiation |
| | last hospitalization (days/ months) | Hospitalization within one month prior to initiation of ARV. Calculated in days and months. |
| | Other drugs (Y) | Prescription drugs for concomitant illness other than ARVs |
| | WHO stage 3&4 | WHO disease staging criteria: stages 3-4 vs. stages 1&2 |
| | IDC attend (Yes) | Attendance of IDC for HIV management prior to initiation of ARVs |
| | Since (days/months) | Refers to the duration of time attending IDC prior to initiation of ARVs (calculated in days and months) |
| | Current TB (Yes) | TB disease at initiation of ARV treatment |
| | Health Problem (Yes) | Caregiver report of child having a health problem at ARV initiation |
| **Caregiver Characteristics** | Biological Parent (Y) | Biological mother and/or father |
| | PMTCT (Yes)[2] | Biological mother's participation in PMTCT programme during pregnancy with index child |
| | age (20-30 yrs) vs. >31 | 20-30 age group vs. <20 and 31-50; 51-60; >60 |
| | Education (Std 10) | Caregivers who completed high school |
| | Post school education (Yes) | Caregivers who pursued post school formal education |
| | Unemployed (Yes) | Not in full-time or part-time employment. |
| | Planning more children | Caregivers reporting intentions to conceive more children than index child |
| | Day care (Bio mother) | Biological mother is the child minder during the day |
| | Depression (>9 cut-off) | Those with CES-D scores > 9 |
| **Socio-economic Characteristics** | Housing (informal) | Those living in mostly self-made informal dwellings (shacks) vs. brick built houses |
| | Sanitation (inside) | Inside water flush toilets vs. outside pit latrines / bucket toilets |
| | Water (outside) | Those who do not have piped running water inside the home but use a communal tap outside. |
| | Housing density | Number of adults and children in the home |
| | Any other infected (Yes) | Having another person in the household HIV infected other than the index child |
| | Grants (Y) | Receiving a social welfare grant from the state (e.g. child care, pension, disability grants) |
| | Significant Life events (Y) | Experiencing significant life events defined as death in family, illness, hospitalization of any household member, retrenchment, employment (after unemployment), divorce/separation, new baby, moving house etc. |
| **Health service characteristics** | Access to ARV clinic (ward) | Those who were referred to IDC via the inpatient wards at RXH vs. those who were referred by primary care clinics |
| | Counselled | Those who received initial counselling regarding ARVs by counsellor vs. doctor or nurse |
| | Referred to IDC for ARVs | Those referred specifically for ARVs to IDC (at a stage when they need it vs. those referred prior to requiring ARVs – for HIV management and follow-up. |

Based on identifying the best predictor of viral load, the measure most highly correlated with virological outcomes was chosen as the most appropriate measure of adherence for use as the adherence measure in the analysis of associations with adherence.

Several variables, indicating disease severity (see Table 3.7), were analyzed for association with viral load since these were hypothesized to potentially influence viral load outcome (see Appendix 8). Bivariate analyses were conducted both for association with viral load and for tests of co-linearity between variables, using chi-square tests. Viral load data was skewed and thus log transformed to the base 10.
Z-scores for anthropometric measures were calculated using EPI INFO (EPI NUT), Centre for Disease Control (CDC) version 2000.



**Table 3.7: Proxy variables indicating disease severity**

| Variable | Definition |
|---|---|
| Height-for-Age Z-score | Indicating stunting |
| Weight-for-Age Z-score | Indicating wasting |
| 'Health problem' | Caregiver report of child being ill at initiation of ARVs |
| 'Recent sickness' | Acute illness within one month prior to commencement of ARV treatment |
| 'Recent hospitalization' | hospitalization within one month prior to ARV initiation |
| 'Current TB' | TB disease at ARV initiation |
| WHO staging | stages 3 & 4 |
| 'Other drugs' | Taking other prescription drugs for concomitant health conditions at initiation of ARVs |
| Baseline viral load measure | The viral load measure taken prior to initiation of ARVs |

Bivariate analyses were conducted as follows: t tests were used to compare the adherent ($\geq$95% doses taken based on caregiver self-report) and non-adherent participants on continuous variables and chi square tests, generating odds ratios and p-values with 95% confidence intervals, were used for dichotomous variables.
Four approaches were used to analyze the CES-D scores. (1) The use of the traditional cut-off of 16 to identify women at risk for depression; (2) The use of a cut off of 10 based upon findings of Brandt (2007);(3) The use of CES-D scores as continuous data in multivariate modelling, without dichotomization into depressed

vs.non-depressed. (4) The identification of the cut-off for the present study as defined by Radloff (1977). These results are described in chapter 4.

Cumulative scores were calculated as follows: sum CES-D (score Month 1 + Month 3+ Month 6) divided by 3; where data was missing the scores were divided by the number of completed months for which data was available.

For the MOSSSS, the mean of total raw scores for perceived support and total satisfaction scores were calculated. In addition, mean scores were determined for each of the four sub-domains. These scores were not dichotomized but were treated as continuous in the bivariate and multivariate analyses.

Power calculations were conducted for each variable included in the regression analysis to determine whether the study had sufficient power to detect significance at the level of Alpha 0.05 if the hypothesized odds ratios were true (Table 6.4 in chapter 6).

The 'repeated measures' analysis approach was not used despite measures at baseline and treatment months 1, 3 and 6, due to the fact that viral load outcome was only available at one time point, namely, 6 months. However, paired t-tests were conducted on selected variables, where changes over time were hypothesized to influence adherence such as the CES-D (depression), food security, MOSSSS, (social support) scores and significant life events, to determine whether changes in scores between month 1 and month 6 were statistically significant.

Several logistic regression models were fitted using stepwise forward and backward analysis in order to test the strength of association of variables, identified in bivariate analysis as having an association with the measure of outcome (adherence). These variables were grouped into the four domains (child, caregiver, socio-economic and health systems characteristics). Adherence was dichotomized with 1= $\geq$95% (good adherence) and 0= <94% (poor adherence). In this way the 'best' model was chosen on the basis of the most plausible, clinical implication, guided by the odds ratios of the statistically significant variables.

## 3.9. Ethical Considerations

***Consent and Confidentiality***

Permission to conduct this research was obtained from the Provincial Department of Health, Western Cape and the Red Cross Children's War Memorial hospital. Written, informed consent was obtained from each respondent for participation in the study.

Participation was voluntary and non-participation in the intervention by eligible patients did not compromise their access to treatment. Only one caregiver refused to participate. There were four patients who defaulted from the clinic and thus the study. Patients were considered defaulters in the study if they missed an appointment and could not be contacted within two months of the missed appointment. A further two patients were very late for their appointments but returned within the 2 month period and were therefore not considered to be defaulters.

All patient data were entered into the database using unique enrolment numbers to link the data. Data capture sheets contained patient identifying information in order to link the laboratory results to the patient data. All confidential information relating to the study was held in a lock up facility at the site and computerised data were managed by the Principal Investigator only. No patient identifying details will be revealed in research reports or scientific publications.

*Benefits*

There were no direct benefits to the patients for participation in this study.
Laboratory results were obtained from routine clinical screening results therefore no invasive procedures were required for this study.

No funding was received for this study and there were no financial benefits to patients. Participants were interviewed during their routine clinic appointment. Children were given a sweet by the research assistant and allowed to play with the toys or draw, depending on their age (in the same room) during the interview.

Caregivers, who scored high on the depression scale, were asked whether they wanted a referral to the hospital social worker. In all cases the caregivers were willing to speak to the counsellor about what they thought was causing their symptoms and only one participant required further management by the social work department. This discussion usually took place after the interview, after the screening instrument was scored by the researcher. However, the interviewer was trained to score the questionnaire and if it appeared that the score was high, he/she would score immediately and discuss with the caregiver directly after the interview.

When poor adherence or incorrect dosing was noted by the researcher, the caregiver would firstly be informed and the details solicited. Thereafter, the information would be noted on the patient folder and the patient would be referred for further management to members of the health care team.

***The Helsinki declaration***

This study was carried out according to the ethical principles set out in the World Medical Association's Declaration of Helsinki as amended in October 2000 (WMA General Assembly, 2000) and in compliance with the National Health Act (Act No. 61 of 2003). The researcher has certification in "Protection of Human Participants in Biomedical and Behavioural Research", obtained on the 7 September 2001 at Columbia University's Health Sciences Division.

Approval for this study was obtained from the Research Ethics Committee of the University of Cape Town as well as the Dissertation Committee (ref: 256/2004 dated 30 August 2004). (Appendix 1)

# CHAPTER 4
# RESULTS PART 1: COHORT DESCRIPTION

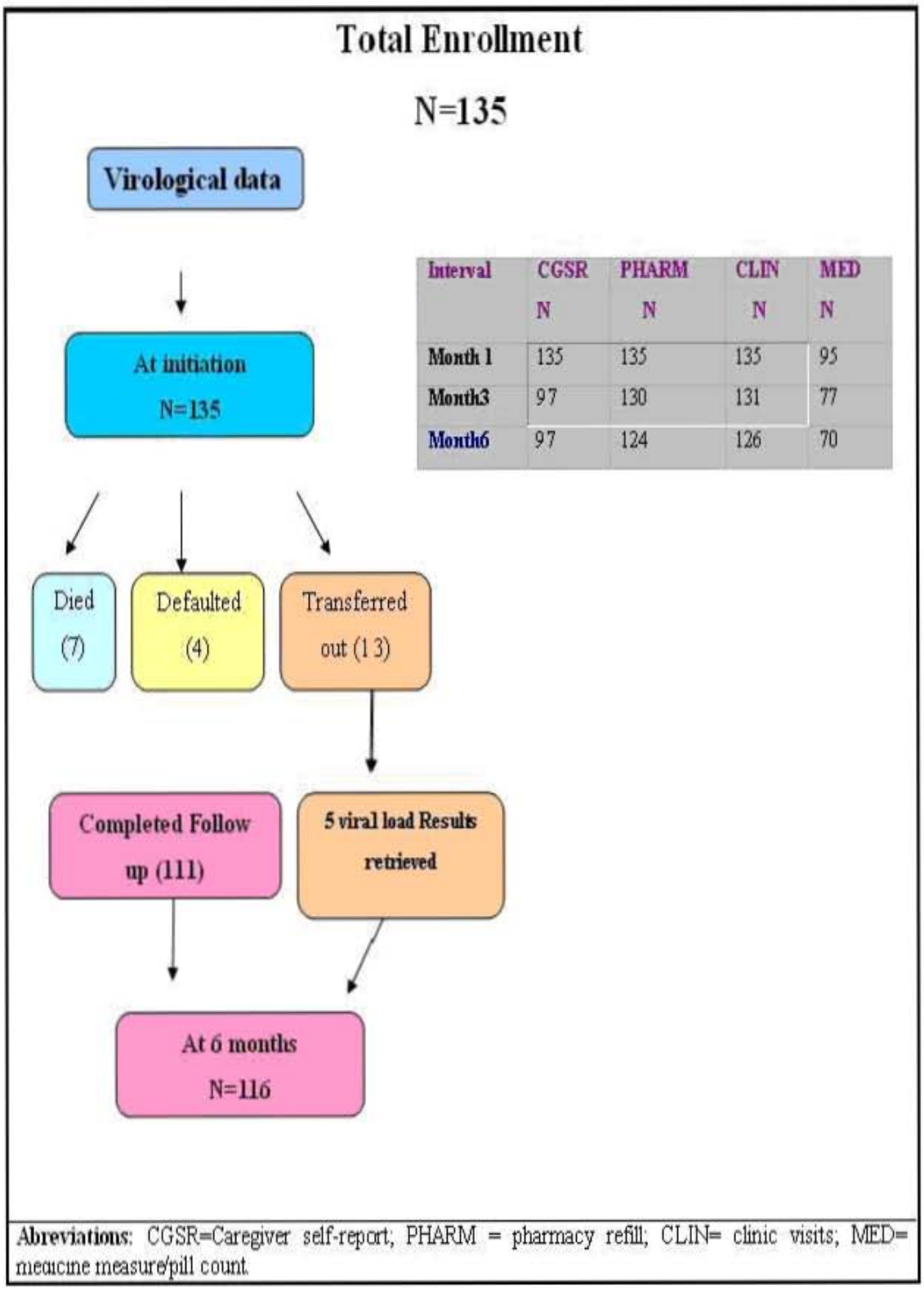
## 4.1. General Overview of Results

The results section is divided into three parts viz. Part 1: Description of the cohort, Part 2, Adherence measurement and Part 3: Factors influencing adherence.

Part 1 deals with the first aim of the analysis to describe the cohort. Part 2, deals with the determination of which adherence measure best predicts the viral load outcome and how each measure agrees with the other. The four measures of adherence used in this study were pharmacy refill; clinic visits; caregiver self-reported adherence and medicine measure/pill counts. Data were collected at Months 1, 3 and 6 of treatment. Part 3 deals with determination of which factors influence the adherence outcome.

Data on pharmacy refill and clinic visits were available for 135 children, with the death of 7 children during the follow-up period. Data on caregiver self-report were available for 135 caregivers at interval 1 (month 1) and 97 caregivers at intervals 2 (month 3) and 3 (month 6). Medicine measures/pill counts were available for 97 children for intervals 1 to 3. CD4 and viral load results at 6 months were available for 116 of the 135 children (Figure 4.1). Analysis of adherence measures was based on averaged cumulative rates, not repeated measures, because there was only one outcome measure, namely, viral load count at 6 months (see chapter 3 for details of formulae to calculate adherence).

**Figure 4.1: Cohort Attrition and Sample size for each measure**




| Interval | CGSR N | PHARM N | CLIN N | MED N |
|---|---|---|---|---|
| Month 1 | 135 | 135 | 135 | 95 |
| Month3 | 97 | 130 | 131 | 77 |
| Month6 | 97 | 124 | 126 | 70 |

4.2. Descriptive Data on Cohort characteristics

Demographic and other details were available for 135 children. A description of the cohort is preceded by the presentation of the cohort follow-up results. Objective 1 is addressed at the end of this chapter with the description of adherence for the various measures.

## 4.3. Follow-up Outcomes of children enrolled into the study

One hundred and thirty five children on treatment were enrolled into the study during the period 1 October 2004 to 30 June 2006, followed up for 6 months respectively. Two of the children were siblings and therefore had the same caregiver. One sibling was initiated on treatment a month after the first one. By the end of the follow-up period thirteen children were transferred from RXH to primary care clinics for antiretroviral treatment follow-up (viral load results were obtained from five of these children and form part of the analyses); seven children had died; four children had defaulted treatment and could not be traced. Defaulters were defined as those children not returning for clinic follow-up after missing one clinic appointment and not being contactable after one month through telephonic and home visit follow-up by clinic staff (which meant they did not return for clinic appointments or medicine refills for 2 months). The remaining one hundred and eleven children were attending the IDC clinic for antiretroviral treatment (see Table 4.1) at six months of treatment.



**Table 4. 1: Status of cohort at the end of the follow-up period**

| Outcome | Frequency | % |
|---|---|---|
| Alive on HAART | 111 | 82.22 |
| Defaulted | 4 | 2.96 |
| Died | 7 | 5.19 |
| Transferred Out | 13 | 9.63 |
| **Total** | 135 | 100 |

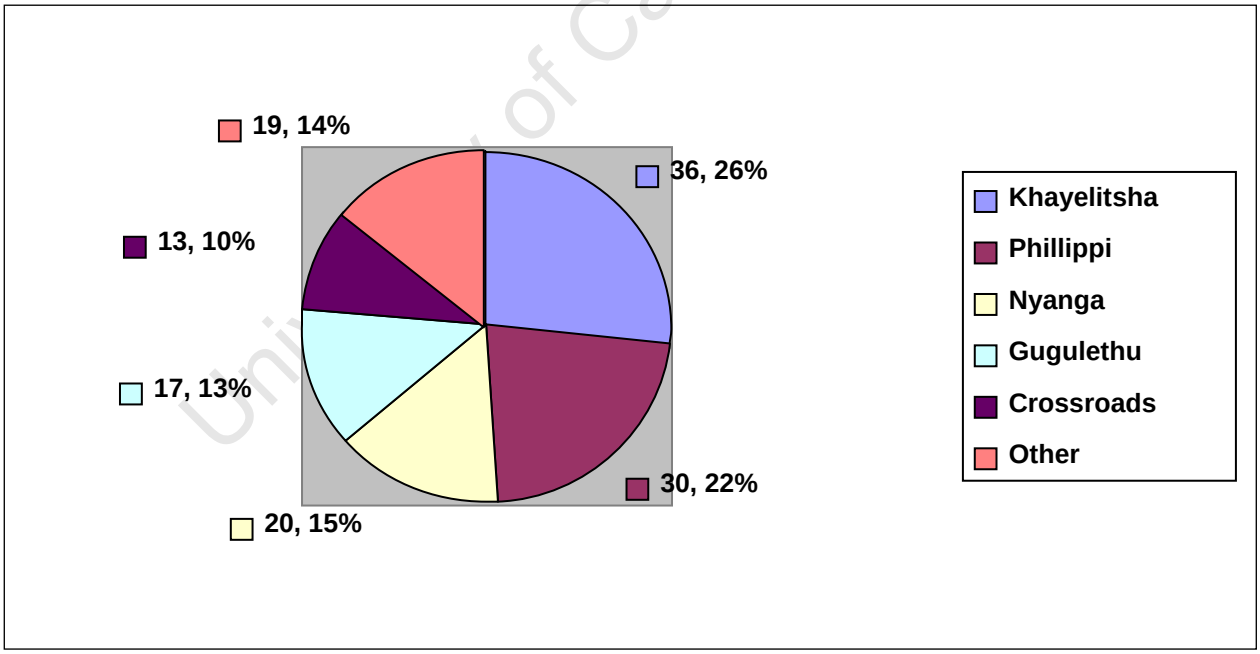
## 4.4. Socio-economic characteristics

### 4.4.1. Areas of Residence

More than half of the cohort lived in the suburbs of Khayelitsha and Phillippi (67%). The largest proportion (36%) lived in Khayelitsha. This is a peri- urban area approximately 35kms away from RXH, covering an area of approximately 15km$^2$ and home to approximately ½ million people. The many people living in Khayelitsha originate from the Eastern Cape Province and often travel between the Western Cape and Eastern Cape, throughout the year but particularly during the Christmas holidays.[37] Phillippi, Nyanga and Gugulethu were the main areas where the rest of the cohort lived (see Figure 4.2). These areas are of similar demographic profile as Khayelitsha with high rates of unemployment and informal dwellings.



**Figure 4.2: Distribution of participants according to Residential Areas (N=135)**




'**Other**' = Belthorn (1) Bloekombos (1) Delfdt (1) Driftsands (1)Du Noon(4) Langa (3) Muizenberg(1) Westlake (1) Woodstock (2) Rondebosch(1) Grassy Park(1)

[37] This information is relevant to service delivery. Often patients who have access to fridges in town need to have their medication changed when they go to the E.Cape for extended periods, especially over xmas, or for funerals or other family occasions, where they may not have access to a fridge.

### 4.4.2. Housing and Sanitation

Approximately 55% (74/135) of families lived in informal dwellings (self-made wood and iron structures) and approximately 53% having no piped water inside the dwelling. Only 33% (45) of families had an inside flush toilet despite 45% reporting that they lived in formal dwellings (brick dwellings). The remaining number of respondents reported using outside pail toilets.

### 4.4.3. Household Density

Housing density ranged from 1-18 adults per dwelling and 1-10 children per dwelling. However, the mean housing density for adults was 3 and for children, 2. Thus, household density was a median of 4 (IQR 3-6) and a mean of 5 (sd: 2.59).

### 4.4.4. HIV infection in the household

In response to the question "Are any other household members HIV infected", sixty nine (51.11%) affirmed that other household members, other than the index child were infected with HIV. Sixty two (45.93%) said "No" while only four (2.96%) reported that they did not know the status of other household members.

### 4.4.5. Disclosure of HIV status and Experience of Stigma

Caregiver reported that none of the children in this cohort had been told that they were infected with HIV. Disclosure to the child was not applicable to the majority of children (67.4%) in this cohort who were younger than three years of age (mean age 27.08 months).

For those older than three years, caregivers reported that they had difficulty in initiating the process of disclosure with their children and chose to focus on the somatic symptoms of the child as reasons for giving the medication.

Children between the ages of three and seven years in the cohort were given some of the following reasons for taking ARVs:

*"I tell him he has chest problems*"[ caregiver of a 5 year old];
*"I tell him he is sick*"[caregiver of a 4 year old]
"*I told her she has pneumonia*"[caregiver of a 6 year old];
*"I tell him that he has TB*"[caregiver of a 6 year old];
*"I told her it is for her ear problems*"[caregiver of a 5 year old].

Several caregivers expressed the opinion that the child was too young (despite the fact that there were children >5yrs in this cohort) and didn't know anything about HIV and some reported that their children had not started asking any questions about it yet. Caregivers were more likely to disclose the child's HIV status to other family members (60.74%) than friends and neighbours (8%). However, twenty nine (21.48%) respondents reported that only they and their partners (the biological parents of the child) were aware of the child's status while thirteen (9.63%) had not told anyone else, not even the biological father of the child.

Only 8% reported that they had chosen to tell friends/neighbours including a foster parent who had told her pastor and all her family members about the child's HIV status. Of those who had disclosed, only ten respondents (7.41%) reported that they experienced adverse reactions after disclosure.

Some of the adverse reactions included the following stories:

***"…my cousin didn't want her child to play with mine. I left and went to live alone"*** *(biological mother of a 21* month old child);

***"…the biological mom abandoned child and father when she discovered their status, we have never heard from her again"*** (stepmother of a 6 month old baby);

"…after the death of my mother, the family would not take care of us ***anymore because we here HIV positive, we had to leave the house"*** (the mother of a 19 month old baby);

***"…when I told him [partner], he ran away from us at the time I felt like dying but we have managed without him"*** (mother of a 6 year old boy).

### 4.4.6. Household Food security

In response to the question, "In your opinion, has there been sufficient food to satisfy the child's appetite?" more than 80% reported that they thought there was sufficient food in the household over the follow-up period. Table 4.3 illustrates that the response of those who answered at each interval suggested an increase in report food sufficiency over time. However, the results of paired t-tests showed no statistical differences between the mean affirmative responses at the three points in time (Table 4.2). However, the frequency of responses regarding insufficient food supply decreased over the 6 month period from 12 in month 1, to 5 in month 6 (Table 4.3).

**Table 4.2: Paired t test results: Food security over time**

| Period | N | Mean difference | Std Error | CI | t | Pr(T <t) |
|---|---|---|---|---|---|---|
| Month 1 and Month 3 | 84 | 0.12 | 0.05 | -.086 ;0.11 | 0.24 | 0.60 |
| Month 3 and Month 6 | 69 | 0.58 | 0.05 | -0.15 ; 0.03 | -1.27 | 0.10 |
| Month 1 and Month 6 | 75 | -0.05 | 0.04 | -0.14 ;0.03 | -1.27 | 0.10 |



### 4.4.7. Significant Life Events

Significant life events were defined as events affecting the family such as funerals, hospitalizations, illness of primary caregiver, illness of a sibling of the index child, illness of other family members whom the caregiver had to look after and retrenchments. "Other" responses specified by the respondents included; having a baby, moving house, separating from spouse/boyfriend and finding employment. Between 24% and 30% of respondents reported experiencing a significant life event during the follow-up period.

**Table 4.3: Summary Food security and significant life events over time**

| | Month 1 | Month 3 | Month 6 |
|---|---|---|---|
| **Food security** | | | |
| Observations | 93 | 87 | 77 |
| Yes (enough) | 81 (87%) | 77 (88%) | 72(94%) |
| No (not enough) | 12 (13%) | 11 (12%) | 5 (6%) |
| | | | |
| **Significant Life Events** | | | |
| Observations | 94 | 88 | 78 |
| Yes | 23(24.5%) | 24(27%) | 23(30%) |
| No | 71(75.5%) | 64(73%) | 55(70%) |

## 4.5. Caregiver Characteristics

### 4.5.1. Caregiver Relationship to the child

One hundred and thirty four caregivers represented 135 children (two children were siblings). Approximately eighty six percent of primary caregivers were biological mothers (N=115) the remainder being grandmothers (7.5%), aunts (4.5%) and foster parents (2.2%). Of the children not having a biological mother as primary caregiver, two (10.5%) were abandoned and 12 (63%) were orphaned.

Four percent (N=6) of children had biological mothers living elsewhere (not involved as primary caregivers). It should be noted that children living in residential care (children's homes) were excluded from participating in the study (see Chapter 3: section 3.7.1).

### 4.5.2. Age

Caregivers were asked to categorize themselves into one of the following age categories: Under 20; 20-30; 31-40; 41-50; 51-60 and >60 (Table 4.4). Data were available for 134 caregivers. The majority of caregivers (61%) were in the 20-30 year age category.

**Table 4.4 Caregiver Age distribution**

| Age Category (Years) | Frequency N | % |
|---|---|---|
| **Under 20** | **2** | **1.5** |
| **20-30** | **82** | **61.2** |
| **31-40** | **39** | **29.1** |
| **41-50** | **5** | **3.7** |
| **51-60** | **2** | **1.5** |
| **60 and over** | **4** | **3.0** |

### 4.5.3. Education

The majority of caregivers reported that they went to high school. One hundred (74.07%) caregivers reported completing senior high (standards 8-10/ Grades 10-12). Of these, forty (30%) reported passing the highest standard (standards 10/ Grade 12). Twelve (9%) reported no high school attendance while three (2%) reported absolutely no schooling.

### 4.5.4. Marital Status

Approximately 42% of caregivers were married/ living with a partner while 53% reported never being married. The remaining number of caregivers reported that they were divorced (2%), separated (1.5%) or widowed (1.5%).

### 4.5.5. Caregiver Employment status and Sources of Income

The majority (75.6%) of caregivers reported that they were unemployed, while only 13% reported having formal employment. The rest of the sample reported casual employment (8%) and running a home-based small business/spaza shop (3%).

Approximately 41% (N=54) of caregivers reported that their spouses/partners provided financial support to them and their child while 34% (N=45) reported to be the sole providers. The remaining caregivers were supported by parents and other family members 26% (N=35).

Sixty percent of caregivers reported receiving some form of social security grant. The largest proportion of social security grants (86%) were childcare dependency grants. The rest were derived from old age pension grants (5%), disability grants (6%) and foster care grants (3%).

### 4.5.6. Caregiver Health Status

Regarding the caregiver's knowledge of their own HIV status, 81 % (N=109) reported that they knew their status and of these, 90% (N=98) were HIV-infected.
Approximately 8% (N=10) caregivers were on antiretroviral treatment (for themselves). A further 8% (N=11) reported that they suffered with chronic health problems other than HIV infection. These included conditions such as arthritis, hypertension and asthma. One caregiver reported being on tuberculosis (TB) treatment for the second time. Twenty percent (N=27) reported that they had previous TB.

### 4.5.7. Caregiver Mental Health and Social Support

#### 4.5.7.1. Depression

In order to identify symptoms of depression among caregivers we used the Centre for Epidemiologic Studies for Depression (CES_D) depression screening tool. Analysis of the cumulative CES-D scores for intervals 1, 2 and 3 for this cohort, resulted in a mean score of 5.2 with a range between 0 and 52 at interval 1. CES-D scores declined over time with a mean of 4.45 at interval 2 and 3.5 at interval 3 with a corresponding decline in the maximum range from 52 at interval 1 to 33 at interval 3 (Table 4.5), indicating that depressive symptoms amongst caregivers declined as children's duration on ARV treatment increased between 1 and 6 months. However, analysis using a matched pair t-test (Table 4.7) resulted in no statistically significant difference between the mean scores at months 1 and 6 (mean difference= 1.18; p=0.12). Similarly, the difference in means of CES-D scores between months 1 and 6 was 1.75 but this was not statistically significant either (p=0.09). The finding regarding lack of significant difference between the means at the two time points may be a result of

observation attrition from month1 to month 6. On closer examination, the 16 missing observations at month 6 included observations with the highest CES-D scores at month 1(e.g. max. 52 at month 1, missing at month 3) which accounted for the higher mean at month 1.

**Table 4.5: Mean CES-D scores at Treatment months 1, 3 and 6**

| Variable | N | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|
| CES-D Month 1 | 92 | 5.24 | 1.5 | 9.06 | 0 | 52 |
| CES-D Month 3 | 85 | 4.46 | 1 | 7.77 | 0 | 38 |
| CESD Month 6 | 76 | 3.50 | 1 | 6.10 | 0 | 33 |

To determine whether there was any significant difference in CES-D scores from month 1 to month 6, for the cohort who remained till 6 month follow-up, the mean scores for each interval were calculated. The results are in Table 4.6.

**Table 4.6: Mean CES-D scores at Treatment months 1, 3 and 6 for caregivers remaining till 6 month follow-up**

| Variable | N | Mean | Median | Std. Dev. | Min | Max |
|---|---|---|---|---|---|---|
| CES-D Month 1 | 72 | 4.11 | 1 | 7.09 | 1 | 44 |
| CES-D Month 3 | 67 | 4.40 | 1 | 7.21 | 1 | 30 |
| CES-D Month 6 | 72 | 3.50 | 1 | 6.10 | 1 | 33 |

The mean CES-D score at month 1 for those with missing values at month 6 (N=20), was 9.3 with a median score of 3 (SD= 13.51) in comparison to those (N=76) for whom data was not missing (mean =4.1 and median=1(SD= 7.09).

There was 20% attrition between months 3 and 6 from those with scores at both intervals (Table 4.5). The mean CES-D score at month 3 for those (N=18) who had missing data at month 6, was 4.6 (SE: 2.32; CI -.22; 9.5) compared to those who did not have missing data (N=76) and had a mean of 4.40 (SE: 0.88; CI: 2.6; 6.1).

Evidence from paired t-tests indicate that there was a slight difference in mean scores between months 1 and 6 for those who had data at both intervals, however this difference did not reach statistical significance (Table 4.7).

**Table 4.7: Comparison of Mean CES-D scores: Results of Matched paired t-tests**

| Variable | Observations | Mean | Std Err | 95% Confidence Interval |
|---|---|---|---|---|
| CES-D month1 | 72 | 4.11 | 0.83 | 2.45; 5.77 |
| CES-D month 6 | 72 | 2.93 | 0.59 | 1.74; 4.11 |
| Difference in means | 72 | 1.18 | 1.01 | -0.84; 3.20 |

Degrees of freedom= 71 ; t = 1.16; Pr(T > t) = 0.12

*CES-D Score thresholds indicating depressive symptoms*

As indicated in chapter 2, cut-off scores indicate severity of symptoms. In this study four approaches were used.

Scores >15, indicating caregivers with depressive symptoms, were found among 9.78% (9/92) caregivers at month 1; 9.41% (8/85) at month 3 and 3.95% (3/76) at month 6. There was no statistically significant difference between groups at month 1 and 6 (p=0.09). Biological parent status was not significantly associated with depressive symptoms (using the >15 cut-off) at month 1 (Fisher's exact = 0.62; one-sided Fisher's exact =0.41).

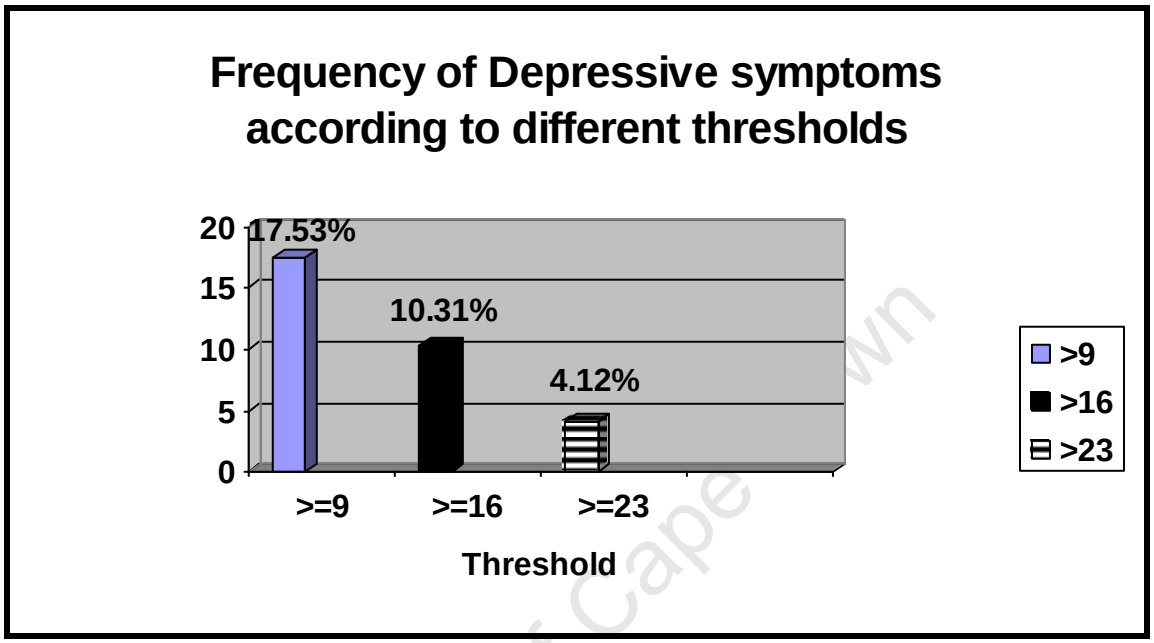
Using a higher threshold with a score of >23 resulted in a prevalence of 4.35% (4/92), 5.88% (5/85) and 2.63% (2/76) respectively. There was no statistically significant difference between groups at intervals 1 and 3 (p= 0.28).

Using the approach based on (Radloff 1977)'s definition as outlined in Chapter 3,[38] the cut-off score for depressive symptoms in this cohort was >9, which was similar to Brandt's Cape Town study. Indicating that amongst these cohorts, scores >9 indicated depressive symptoms requiring referral or attention. In this study, the cut-off was identified using the cumulative CES-D scores, as opposed to (Brandt 2007)'s study which was cross-sectional. Graph 4.1 illustrates the frequency of depressive symptoms among caregivers in the sample at different thresholds.

[38] The cut-off is defined as "that score that identifies the upper 20% of the distribution".

No association was found between HIV positive status of the caregiver and depression (Pearson $\chi 2^{=} 0.11$; p= 0.74).

**Graph 4.1: Frequency of Depressive symptoms among caregivers**






In the present study a Cronbach's Alpha of 0.82 was established, indicating good internal consistency.

*Social Support*

Using the Medical Outcomes Survey of Social Support tool perceived availability of social support among caregivers was determined. The tool considers four domains of social support, namely: tangible support, affectionate support, positive social interaction and emotional/ informational support and scores can vary from zero to 100. In this study, the cumulative mean scores across the four domains were very high (see Table 4.8).

Perceived social support and satisfaction did not relate to the *size* of the respondents network (the number of people specified by the respondent as providing the support), but rather to the *quality* of perceived support from those from whom the support was received. The median number of close friends or relatives from which this support

was derived was 2 (S.D 3.35; IQR 2-3) ranging from 0 to 34[39] close friends or family included. The difference between mean scores at baseline and at 6 months (-3.45; N=60) were statistically significant (Pr (T< t) = 0.001), indicating increased perception of social support at 6 months.

The mean month 1 score for the 20 respondents with missing data at month 6, was 92.45 (SE: 3.74) vs. 96.74 (SE: 1.22) when compared with the 60 respondents for whom data were available at months 1 and 6. These results indicate that those who were not available for follow-up at 6 months had lower perceived social support at month 1 than those who were available for follow-up.

One hundred and ten (81.48%) respondents perceived the members of their household as supportive and helpful. Seventy eight (52.1%) had family living close by who were supportive and helpful while seventy three (54.48%) also had friends living close by who were supportive and helpful. Forty-four percent (N=60) of the sample attended support groups on a regular basis.



**Table 4.8: Perceived availability of social support across the four domains**

| | **Total** **%** | **Tangible support** **%** | **Affectionate support** **%** | **Positive social interaction** **%** | **Emotional/ informational support** **%** |
|---|---|---|---|---|---|
| Mean* | 95.89 | 95.41 | 96.05 | 95.36 | 96.14 |
| Median (IQR) | 99 (93-100) | 100(92-100) | 100(100- 100) | 100(95-100) | 100(92.5 – 100) |
| Std. Deviation | 9.28 | 10.2 | 10.10 | 10.39 | 8.93 |
| Minimum | 24.5 | 20 | 20 | 22.5 | 30 |
| Maximum | 100 | 100 | 100 | 100 | 100 |

***** These are cumulative scores

Table 4.9 below illustrates the depression and perceived social support indicators over time. The data show a steady decline in the mean depression scores over time but no statistical significant difference in means between baseline and month 6 were found (t = 1.12 ; p=0.26). In contrast, perceived social support scores increased over time and the change from baseline to 6 months was found to be significant (t= -3.45; p=0.001).

[39] This number was verified by the researcher – the respondent stuck by her response that this was the number of close friends and relatives in her circle of support. Thus this was an 'outlier'

**Table 4.9: Depression and Social Support indicators over time**

| | Baseline | Month 1 | Month 3 | **Month 6** |
|---|---|---|---|---|
| **Depression*** | | | | |
| Yes | 14 | 15 | 10 | **8** |
| No | 66 | 77 | 75 | **68** |
| Observations | 80 | 92 | 85 | **76** |
| Mean (SE) | 5.40 (0.87) | 5.24 (0.94) | 4.46 (0.84) | **3.5 (0.70)** |
| **Difference in Means baseline & 6 months?** | t = 1.12 (N=63) (pr\| T> t\| =0.26) | | | |
| **Perceived Social support** | | | | |
| Observations | 78 | 80 | 85 | 75 |
| Mean (SE) | 93.73(1.33) | 95.41 (1.31) | 96.74 (1.13) | 98.84 (0.52) |
| Difference in means baseline and 6 months? | t = -3.45 **(N=60)** (pr \|T>t\|)=0.001 | | | |

*Depression indicated by > 9 score

## 4.5.8. Fertility Plans and participation in PMTCT programme

The majority (62.96, N=85) of caregivers reported that they had no plans to have any more children in the future while approximately 23% (N=31) said that they would like to have more children.

Approximately 36% (N=48) of the biological mothers reported that they participated in the PMTCT intervention for the birth of the index child. Two (1.5%) were not sure whether they had received any intervention while the majority (49%, N= 66) reported that they did not. Of note is that approximately 16% (N=19) of those planning to have more children did not participate in the PMTCT intervention for the index child, including those who were not sure whether they had received any intervention. However, there was no statistically significant association between PMTCT participation and planning to have more children (Pearson $X^2$ (1df) =0.3941; p =0.53)

## 4.5.9. Caregiver perception of reason for ARV treatment initiation

Most caregivers (78.5%) responded that the child was sick and therefore doctors recommended that the child start treatment. However, one (0.74%) caregiver reported that she did not know why the child was on ARVs and twenty-two (16.3%) responded

that they didn't think that their child was sick but the doctors said the child should start treatment. Six (4.4%) reported that they had asked the doctors to initiate treatment.

### 4.5.10. Caregiver knowledge and attitude to ARVs

While most of the respondents understood the basic facts about ARV treatment (Table 4.10) and few reported that their child had experienced side effects during the first month of treatment, only 26% were familiar with the names and doses of the child's ARV regimen by 1 month. The amount of respondents (96.7%) who believed that the benefits of ARVs outweighed the risks did not match those with a belief in a good prognosis for their children. Seventy-two (57.6%) expressed the concern that their children may not live long enough to complete their schooling.

**Table 4.10: Knowledge and Attitudes towards ARV treatment**

| Questionnaire response | Number of respondents N= 125 (%) |
|---|---|
| Believe it is good to give child a break from ARV treatment | 3 (2.4%) |
| Take child to traditional healer regularly | 3 (2.4%) |
| Always give ARVs exactly the same time each day | 123 (98.4%) |
| Believe that all three ARVs should always be given and none left out. | 124 (99.2%) |
| Know all the names and doses of child's regimen | 32 (25.8%) |
| Believe treatment should not be stopped when child gets better | 123 (98.4%) |
| Believe that ARV treatment can cure HIV | 12 (10%) |
| Believe that ARV treatment is lifelong | 125 (100%) |
| Believe the benefits of ARVs far outweigh the risks | 120 (96.7%) |
| Believe child will get sick/ medicine will stop working/ viral load will increase if more than 3 doses are missed a week. | 124 (99.2%) |
| Concerned about the child living long enough to complete school | 72 (57.6%) |
| Child experienced side-effects | 38 (30.65%) |



## 4.5.11. Medication administration

The primary caregivers reported that they were mainly responsible for giving the medication and sixty one (45.2%) reported that they had no one else to rely on to give the medication. Nineteen (14%) relied on the child's father, twenty-three (17%) relied on a grandmother while ten (7.4%) relied on the child's sibling to assist with medication administration. The remainder relied on friends (3), a nanny, nurses[40] (8)

[40] These were children who were either still in hospital or in respite care (Temba Care ).

and aunts/uncles (9). In one case, the grandmother considered herself the primary caregiver because the biological mother was still at school but the biological mother lived in the home and would assist with administration.

Table 4.11 illustrates that grandmothers who were the primary caregivers of the children, were more likely to rely on someone else to assist with medication administration than biological mothers, foster parents or aunts. In other words, the grandmother brought the child to the clinic, took care of the child during the day and lived with the child but would rely on another member of the household, notably, her own daughter (sibling of the child's biological mother who died) to give the child the medication.

**Table 4.11: Person responsible for medication stratified by Primary Caregiver Status**

| Primary Caregiver status | Aunt | Both Parents | Foster Parents | Grandmother | Mother | Other | Total |
|---|---|---|---|---|---|---|---|
| **Aunt** | **6** | **0** | **0** | **0** | **0** | **0** | **6** |
| **Foster Parent** | **0** | **0** | **3** | **0** | **0** | **0** | **3** |
| **Grandmother** | **9** | **0** | **0** | **0** | **0** | **1** | **10** |
| **Mother** | **0** | **1** | **0** | **1** | **114** | **0** | **115** |
| **Total** | **15** | **1** | **3** | **1** | **114** | **1** | **135** |



## 4.5.12. Reminder Tools

Participants were asked about their medication administration practices during the week (mornings and evenings) and at weekends (morning and evening) including specifying routines on Saturdays and Sundays.

During **weekday mornings** most caregivers (54%, N=67/125) reported that they relied on cell phone (36%) and clock alarms (18%) to remind them to give medication. Other reminder tools included radio (2.4%, 3/125) and TV (3.2%, 4/125). Approximately 34% (N=42/125) relied on 'routine'[41] or other people to remind them (7.2%, 9/125).

[41] This term 'routine' was explained as the fact that they just remember to take tablets because it fits into the other tasks they do daily – when it 'gets to a certain time they just remember' to give the medication.

There are slight changes in the pattern of use of reminder tools during **weekday evenings** compared to weekday mornings. Fewer **(N=125)** reported reliance on cell phones and clock alarms at night (44% vs. 53%) and more relied on TV programmes (17% vs. 3.2%). Only two reported using the radio, two relied on someone else to remind them; and 36% vs. 34% reported reliance on 'routine'.

## 4.6. Child Characteristics

### 4.6.1. Siblings

Sixty-two (45.9%) children had no siblings. The median number of siblings was 1 (IQR 0-1) with a range of 0 to 7. Only 4.4% (N=6/135) of the children had a sibling who was also HIV infected.

### 4.6.2. Care giving Arrangements

Eighty five (62.96%) children were looked after by their mothers during the day. Twenty-two (16.2%) attended school (N=10/135) or crèche (12/135) while the remainder were cared for by an aunt (5.93%), nanny (2.96%) or a grandparent (9.63%). Only two children (1.48) did not have a consistent day care arrangement and one child was in respite care (Temba Care) for several weeks during the follow-up period.

Only 5 (3.7%) children slept over at another home during the week or at weekends. The majority (92.6%) of caregivers reported that their child never sleeps away from home while four (2.96%) children "sometimes" slept away from home.

### 4.6.3. Age and gender

The mean age of children in this cohort was 27.1 months, ranging from 3.2 to 86.0 months. The median age was 17.7 months (IQR: 9.3 - 37.6). Seventy-four (54.8%) were boys.

### 4.6.4. WHO Staging Criteria

At baseline, the majority (58.5%) were categorized with stage 3 and thirty-eight (28.2%) with stage 2 disease according to WHO staging criteria. Only eighteen (13.3%) were categorized with stage 4 disease at ARV initiation.

### 4.6.5. Growth

***Baseline growth characteristics***

Baseline weight for the cohort ranged from 2.41kg to 22.6kg with a mean of 9.08kg and a standard deviation of 4.39. Baseline height ranged from 49.4cm to 118.6 with a mean height of 75.4cm (sd: 15.79). On average, children in this cohort were 2 to 3 standard deviations below the norm on their anthropometric scores, indicating relatively poor nutritional status at ARV initiation (Table 4.12).

**Table 4.12: Baseline Anthropometric Scores:**

| Variable | N=135 Mean | Standard Deviation | Range | Reference Mean scores(0-59mths) In Africa ** (std.dev) |
|---|---|---|---|---|
| Weight –for-age z-scores | -2.53 | 1.47 | -6.32 - 1.97 | -1.02 (1.42) |
| Height –for-age z-scores | -2.99 | 1.67 | -9.46 – 1.6 | -1.64 (1.74) |
| Weight-for-height z-scores | -0.81 | 1.34 | -3.65 – 4.48 | -0.07 (1.44) |

**source: (World Health Organization 2007)



### 4.6.6. Immunological and virological Features

Baseline viral load results were available for 130 children (Table 4.13). The median log baseline viral load for the cohort was 5.58 copies per ml with a range of 2.68 to 6.86. Viral load results at 6 months were available for 116 children. The median log viral load at 6 months was 1.69 copies per ml with a range of 1.69 to 6.46.

Baseline CD4 data were available for 135 children. The median baseline CD4 % for the cohort was 13%. The median absolute CD4 count was 502. Six-month CD4 data was available for 117 children, with a median CD4percentage of 23% and median absolute value of 1100. These results indicate that there was a good immunological response to treatment within the first 6 months.

**Table 4.13: Immunological and Virological cohort Features**

| Variable | No. of Observations | Median | IQR | Mean (Std. Dev) |
|---|---|---|---|---|
| **Baseline Measures** | | | | |
| Baseline CD4 % | 135 | 13.0% | (8.0 – 18.0) | 14.5 (10.96) |
| Baseline CD4 absolute count | 133 | 502 | (247 -886) | 647.4 (561.9764) |
| Baseline viral load | 130 | 500000 | (130 000-1400000) | 994028 (1197560) |
| Baseline Log viral load | 130 | 5.69 | 5.1 - 6.1 | 5.6 (.76) |
| **6 month Measures** | | | | |
| CD4 % @ 6 months | 117 | 23.1% | (16.4 – 28.9) | 22.90 (8.48) |
| CD4 absolute @ 6 months | 117 | 1100 | (673 – 1434) | 1146.154 (627.3248) |
| Viral load @ 6 months* | 116 | 50 (LDL) | (50 – 430) | 61033.5 (348596.5) |
| Log viral load @ 6 months | 116 | 1.7 | 1.7 - 2.6 | 2.4 (1.2) |

*Maximum viral load @ 6 months = 2 900 000 copies per ml
Abbreviation: LDL= Lower than detectable levels



### 4.6.7. ARV Regimens and concomitant medication at initiation of treatment

HAART was provided by giving three separate ARV medications to each child. In the case of children on TB treatment, a fourth ARV was added to the regimen for the duration of TB treatment[42] for some children in the study only.

All children in this study were on first line regimens since they were all initiated on treatment at entry into the study. The regimens typically consisted of two Nucleoside Reverse Transcriptase Inhibitors (NRTI's) and one Non-nucleoside Reverse

[42] This practice was introduced during the study period. Not all children on TB treatment in this study received this standard of care, most likely due to clinician error.

Transcriptase Inhibitor (NNRTI) or a Protease Inhibitor (PI). The drug regimens[43] are denoted as ARV 1, ARV 2, ARV 3 and ARV 4 in the results and are described in Table 4.14. Thirty-nine (28.89%) children were on TB treatment at initiation of therapy. One hundred and thirty one children (97.4%) were taking cotrimoxazole at initiation of ARV treatment. Only five of the thirty-nine (12.82%) children who were on TB treatment[44] at initiation of ARV therapy received an additional PI[45].

**Table 4.14: Frequency table for ARV Regimens utilized amongst the cohort**

| Drug Name (abbreviation) | Type | Dosing Frequency | Frequency (%) |
|---|---|---|---|
| **ARV 1** | | | |
| Zidovudine (AZT) | NRTI | Twice daily | 46 (34.07) |
| Stavudine (D4T) | NRTI | Twice daily | 89 (65.93) |
| ARV 2 | | | |
| Lamivudine (3TC) | NRTI | Twice daily | 134 (99.26%) |
| Didanosine (DdI) | NRTI | Twice daily | 1 (0.74%) |
| ARV 3 | | | |
| Efavirenz (EFV) | NNRTI | Once daily | 44 (32.59%) |
| Kaletra[46] (KLT) | PI | Twice daily | 47 (34.81%) |
| Nevirapine (NVP) | NNRTI | Twice daily | 19 (14.07%) |
| Ritonivir (RTV) | PI | Twice daily | 25 (18.52%) |
| ARV 4[47] | | | |
| Kaletra | PI | Twice daily | 3 (2.22%) |
| Ritonivir | PI | Twice daily | 2 (1.48%) |

In addition to the twice daily dosing with ARVs, seventy-one children (54.6%) were taking additional medications including antibiotics, medication for asthma and epilepsy and a range of infections but excluding TB.



[43] These regimens were implemented during the period of the study which was 2004 to 2006. This was a period during which provincial policies regarding guidelines for treatment and drug procurement were being developed along with the implementation of the National ARV roll-out programme. It should be noted that a policy on first and second line paediatric ARV treatment was adapted in 2007 being "age" and "history of exposure to perinatal NVP", dependent.

[44] This information was obtained from the patient folder.

[45] The management guidelines for children on HAART receiving TB treatment was implemented to boost the ritonivir since TB medication is known to cause an interaction with Ritonivir (Rifampicin induces cytochrome p450 activity thereby reducing levels of Ritonivir in the body).

[46] Kaletra consists of Lopinivir and Ritonivir (Ritonivir is not active merely to boost the Lopinivir levels).

[47] ARV4 was only given to children on concurrent TB treatment and is no different to ARV 3 – it is merely to boost lopinivir levels (see footnote 43).

### 4.6.7.1. Palatability of ARVs

Most caregivers (93.5%) reported that ARV1 (AZT, D4T) was taken easily. Nearly all (98.4%) reported that 3TC was taken easily (only one child was on Didanosine). Children found the NRTI's (AZT, D4T, 3TC, ddI) more palatable than either the NNRTIs (EFV, NVP) or the PIs (Ritonivir, Kaletra) with the PIs being the least palatable (Table 4.15).

**Table 4.15: Frequency of ARV type and Palatability**

| Drug Name (abbreviation) | Class of Drug | Frequency (%) | Taken easily? (Yes) |
|---|---|---|---|
| **ARV 1** | | | 93.5% (N=116/124) |
| Zidovudine (AZT) | NRTI | 46 (34.07) | |
| Stavudine (D4T) | NRTI | 89 (65.93) | |
| ARV 2 | | | 98.4% (N=122/124) |
| Lamivudine (3TC) | NRTI | 134 (99.26%) | |
| Didanosine (DdI) | NRTI | 1 (0.74%) | |
| ARV 3 | | | 59% (N=73/124) |
| Efavirenz (EFV) | NNRTI | 44 (32.59%) | |
| Kaletra (KLT) | PI | 47 (34.81%) | |
| Nevirapine (NVP) | NNRTI | 19 (14.07%) | |
| Ritonivir (RTV) | PI | 25 (18.52%) | |

### 4.6.7.2. ARV Drug Formulations

The ARV formulations for this cohort consisted primarily of syrups except for Efavirenz which is only available in capsule form but was opened by the caregiver and administered as a solution for children too young to swallow capsules (which were the majority in this cohort), (Table 4.16).

**Table 4.16: Frequency distribution of ARV formulation**

| Drug Name (abbreviation) | Formulation | |
|---|---|---|
| | **Syrups** | **Capsules** |
| **ARV 1 (N=125)** | 99 (79.2%) | 26 (20.8%) |
| **ARV 2 (N=124)** | 122 (97.6%) | 3 (2.4%) |
| **ARV 3 (N=124)** | 80 (64.5%) | 44 (35.5%) |
| **ARV 4 (N=5)** | 5 (100%) | 0 |

### 4.6.8. Hospitalization over time and recent illness prior to ARV initiation

At baseline, 124 children (95.4%) were reported ever being hospitalized prior to treatment but thirty-six, (27.7%) were hospitalized in the month before ARV initiation. Caregivers reported 'recent illness', defined as illness one month prior to ARV initiation, for 40 children (30.8%).

By month 1 of treatment 20% of children were reportedly admitted to hospital since starting ARVs with only one child having two admissions during this period (Table 4.17). The mean duration of hospital stay was 7 days with a range of 1 to 18 days. By month 6 of treatment, five children (6%) were hospitalized in the period between month 3 and 6 with only one child having three admissions during this period. The duration of hospitalization ranged from 2 to 93 days with a mean of 23 days. Only six (6.25%) children had more than one hospital admission during the 6-month follow-up period (a maximum of 2 hospitalizations). The data presented in Table 4.17 shows a decline in hospitalization as well as duration over the 6-month follow-up period.

No association was found between baseline viral load and hospital admission during the 6 month follow-up period by month 1(Pearson $X^2$ (70) = 68.1; p= 0.54); by month 3 Pearson $X^2$ (68) = 72.0; p= 0.35; and by month 6 Pearson $X^2$ (61) = 68.8; p= 0.23). Table 4.17 provides data on hospitalization and duration of hospital stay at each time point. One of the children hospitalized by Month 1 was also hospitalized by Month 6 and 5 children hospitalized by Month 1 were hospitalized by Month 3 as well. While the frequency of hospitalizations among the cohort declined from month 1 to month 6, the few children who were hospitalized by month 6 spent more days in hospital indicating that these were the sickest children with one child having 3 hospital admissions between month 3 and month 6. The number of person days in hospital declined between month 1 and month 6 indicating that duration of hospital stay decreased with duration of ARV treatment during the first 6 months of follow-up.

**Table 4.17: Hospitalization and Side effects over time**

| | Month 1 | Month 3 | Month 6 |
|---|---|---|---|
| **Hospitalization in the preceding interval** | | | |
| Observations | 94 | 88 | 78 |
| Yes | 19 (20%) | 17(19%) | 5 (6%) |
| No | 75(80%) | 72 (81%) | 73 (94%) |
| Mean duration(days) (SE) | 10.16 (1.78) | 6.94 (1.48) | 23.2 (17.56) |
| No. of Person (child) days in hospital | 193 | 59 | 39 |
| Range of no. of admissions per patient | 1-2 | 1-2 | 1-3 |
| | | | |
| **Side effects in the preceding interval**** | | | |
| Observations | 94 | 88 | 78 |
| Yes | 65 (70%) | 49 (56%) | 39 (50%) |
| No | 28 (30%) | 39 (44%) | 39(50%) |

**Reported by caregiver.

## 4.7. Health Service Factors

### 4.7.1. Access to treatment

The majority (74.8%) of children initiated on antiretroviral treatment had a history of attendance at the IDC and only a quarter of the children gained access to treatment through referral from clinics or as in-patients at the hospital.

The original access route to the IDC clinic by this cohort was primary care clinics (34.8%), in-patient referral (54.8%) and self-referral (10.4%). The hospital's in-patient wards form the bulk of the referrals to the IDC clinic.

### 4.7.2. Counselling for initiation of antiretroviral treatment

More than half (52.6%) of the respondents reported that they were given information about ARVs by a lay counsellor. Fifty one (37.8%) reported that a doctor had counselled them while a nurse informed 5%. Six respondents (4%) could not remember who had counselled them.

## 4.8. Adherence Rates

**Objective 1**: To determine the rate of adherence to HAART among the cohort.

Table 4.18 presents a summary of the rates at intervals 1, 2 and 3 according to the four measures. More details about agreement between measures of adherence and the best predictor of viral load are provided in Part 2 of this thesis.

**Table 4.18: Summary of Adherence rates by measures per interval**

| Type of Measure | Month 1 | | Month 3 | | Month 6 | | Cumulative Mean |
|---|---|---|---|---|---|---|---|
| | N | Cohort Mean % (SE) | N | Cohort Mean % (SE) | N | Cohort Mean % (SE) | Sample size; % (SE) |
| CGSR* | 122 | 96.7 (1.2) | 85 | 95.9 (1.8) | 75 | 97.2 (1.22) | N=130; 97% (SE: 8.4); |
| Pharm* | 135 | 89.8 (1.7) | 130 | 80.2 (2.7) | 124 | 84.7 (2.28) | N=135; 85% (SE:17.2). |
| Clin* | 135 | 93.7 (1.3) | 131 | 85.1 (2.7) | 126 | 87.2 (2.22) | N=135; 89% (SE: 16.4) |
| Med* | 95 | 107.0 (3.3) | 77 | 102.9 (4.9) | 70 | 100.0 (2.78) | N=96; 103% (SE:2.05) |

**Note:** Medicine measure/pill count rates are consistently 100% and greater which may be an indication of wastage due to the difficulty of administering syrups (spillage and vomiting of the child), rather than adherence.

***Abbreviations**: CGSR= Caregiver self-report; Pharm = Pharmacy refill ; Clin = Clinic visits; Med= Medicine measure/pill counts

### 4.8.1. Caregiver self-report

The mean cumulative rate of adherence according to caregiver self-report for the 6 month period was 97% (SE: 8.4; N=130).

In response to a specific question "Have you ever missed any doses?" results show that 88% (SE: 0.02) of caregivers reported that their child had never missed any doses.

Twenty six percent of caregivers reported problems with administration. Some of the common reasons for missing doses or problems with medicine administration were: 'ran out of medicine' (3%); 'medicine tastes bad' (10%); 'I forgot' (2%); 'change in

daily routine' (1%); 'child refused to take medicine'(2%); "I'm not always with him/her at the right time' (5 %); 'I was busy with other things (3%) and 'I was ill' (1%).

### 4.8.2. Pharmacy Refill

The mean cumulative adherence rate for pharmacy refill was 85% (SE: 17.22; N=135). Ninety three percent of children had 'on time' pharmacy collections. Only 7% had late pharmacy visits for the period of follow-up. The mean number of days late was 1 day (SE: 6.07) with a range of 0-31 days.[48] Table 4.18 provides the details of mean adherence rates for pharmacy refill for Months 1, 3 and 6.

### 4.8.3. Clinic Visits

The mean cumulative adherence rate for clinic visits was 89% (SE: 16.38; N=135). The proportion of children with 'on-time' clinic visits for the intervals 1, 2 and 3 were 90%, 79% and 77% respectively (Table 4.18).

### 4.8.4. Medicine Measure

The mean cumulative adherence rate for medicine measure was 103% (SE: 2.05;N =96). Syrup formulations were more frequently prescribed for this cohort which accounted for 'over use' due to possible re-administration or spillage. For example, for ARV 1: syrup vs. capsules was 79% vs. 21%, respectively. See Table 4.18 for details of cohort mean adherence rates for medicine measure at months 1, 3 and 6.

This measure was the most difficult measure on which to obtain consistent data due to caregivers not consistently returning medicines for measurement or leaving some bottles at home. Table 4.19 below illustrates the adherence rates per ARV for the cumulative period. It should be noted that the 'bad tasting' medicine such as Kaletra

[48] On-time collections were defined as between 2 days before and up to 2 days after the appointment date. Collections were considered 'early' if collected more than 2 days before the appointment date as defined in Chapter 3.

and Ritonivir had higher rates of adherence (over 100%). The highest adherence rate was for DDI but only one child was receiving this in his regimen. These results demonstrate the challenge of using medicine measure to calculate adherence in a paediatric population using syrup formulations. Forty one percent of the cohort reported that they had difficulty administering the third ARV of their regimen.[49] Except for EFV (a capsule), the cohort all received ARV3 in syrup formulation.

**Table 4.19: Mean adherence rates per ARV (based on Medicine measure)**

| ARV | No. Observations | Cohort Mean % | Std Error | 95% Confidence Interval | |
|---|---|---|---|---|---|
| AZT | 77 | 104 | 5.32 | 93.62 | 114.80 |
| D4T | 156 | 95.05 | 1.82 | 91.45 | 98.66 |
| 3TC | 230 | 105.07 | 3.42 | 98.33 | 111.83 |
| ddI | 3 | 142.18 | 20.72 | 53.02 | 231.34 |
| Klt | 74 | 119.08 | 5.81 | 107.49 | 130.68 |
| Rtv | 37 | 116.63 | 9.00 | 98.367 | 134.90 |
| EFV | 84 | 96.56 | 2.71 | 91.17 | 101.95 |
| NVP | 43 | 98.35 | 3.65 | 90.99 | 105.71 |

Table 4.20. illustrates the frequency of missed doses per ARV by caregiver self-report. The mean adherence rates for Ritonivir and Kaletra were in excess of 115 % respectively, as measured by medicine measure and interestingly, these were also the drugs for which doses were most frequently missed, as measured by caregiver self-report. The other drugs with adherence rates in excess of 100% such AZT, 3TC and DDI did not follow a similar trend as measured by caregiver self-report.



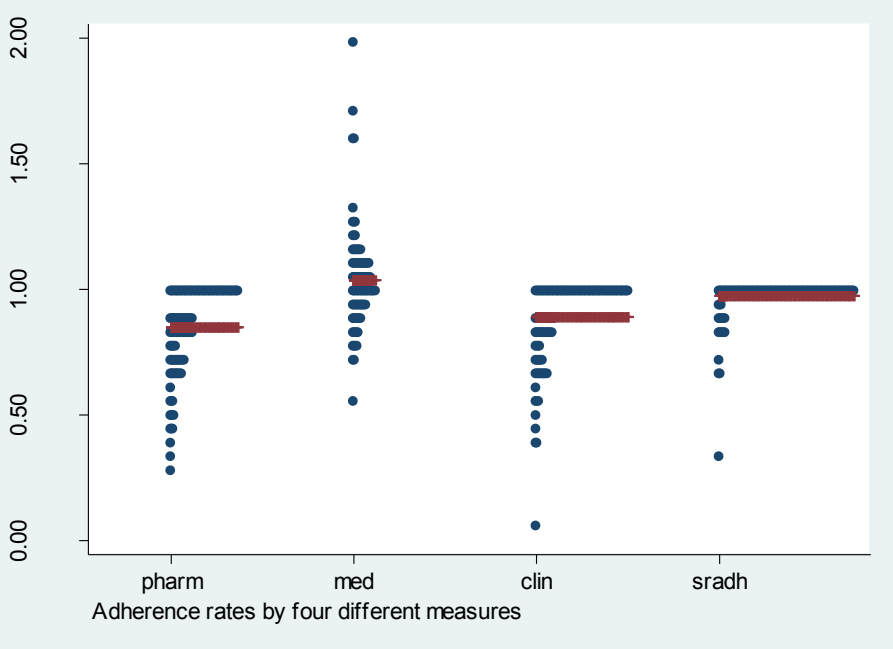
[49] ARV3 consisted of ARVs such as Ritonivir, Kaletra, Nevirapine, and Efavirenz

**Table 4.20: Frequency of Missed doses per ARV by Caregiver Self-report**

| ARV | N | Frequency | % |
|---|---|---|---|
| Lamivudine | 274 | 6 | 2.19 |
| Stavudine | 190 | 5 | 2.63 |
| Efavirenz | 100 | 3 | 3 |
| Kaletra | 97 | 9 | 9.28 |
| Zidovudine | 96 | 3 | 3.13 |
| Nevirapine | 47 | 2 | 4.26 |
| Ritonivir | 44 | 8 | 18.2 |
| Didanosine | 4 | 0 | 0.0 |
| Abacavir | 1 | 0 | 0 |

Finally, Figure 4.3: illustrates the comparison of means by the four different measures, indicating that medicine measure produces the most 'outliers' in the data and among this study population (children), rates tend to be in excess of 100%.

**Figure 4.3: Mean Medication adherence by four measures**




**Abbreviations:** Pharm= Pharmacy refill; Med=Medicine measure/pill counts; clin= clinic visits; sradh= caregiver self-report

In summary, two of the adherence measures (pharmacy refill and clinic visits) measure attendance, while the other two (caregiver self-report and medicine measure/pill counts, measure doses. Determining adherence rates using medicine measure in a paediatric population using predominantly syrup formulations is

problematic since higher adherence rates tend to indicate administration problems rather than adherence per se as is evident when one compares the rates of adherence according to medicine measure (Table 4.19) and the frequency of missed doses per ARV according to caregiver self-report (Table 4.20). For the syrup formulations, the highest adherence rates did not necessarily mean true adherence as is evident by the example of high adherence rates for Kaletra and Ritonivir according to medicine measure but the highest frequency of missed doses reported by caregiver self-report.

# CHAPTER 5
# RESULTS PART 2: MEASURES OF ADHERENCE

**Objective 2**: To determine agreement between the four measures of adherence.
**Objective 3**: To determine agreement of the four measures with virological outcome at 6 months.

## 5.1. Introduction

This chapter reports the results of the analysis of the measures of adherence, addressing objectives 2 and 3 (see box above). In this chapter the following research questions are answered, namely, (1) how do the four different measures of adherence agree with each other? (2) How do the measures agree with viral load at 6 months? In addressing the second question, factors hypothesized to influence viral load were analyzed in order to adjust for covariates in determining the correlation of measures with 6-month viral load.

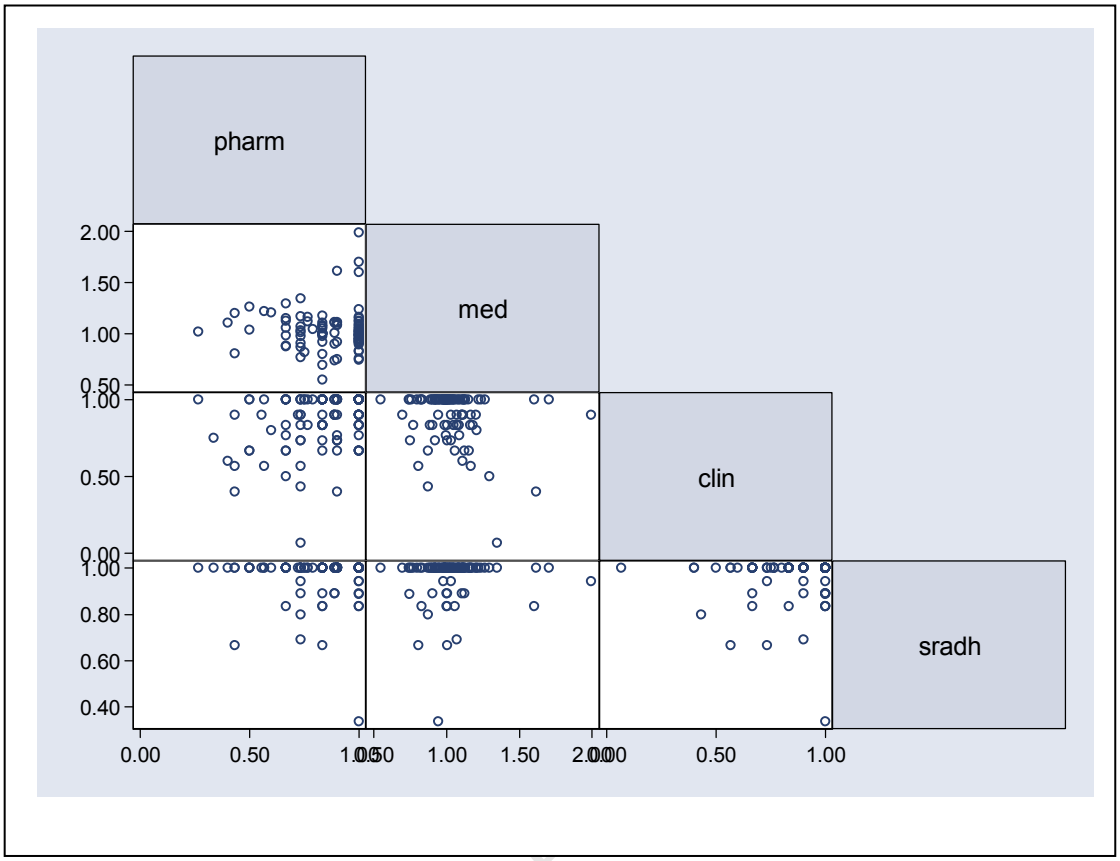
The four measures of adherence used in this study were pharmacy refill; clinic visits; caregiver self-reported adherence and medicine measure/pill counts.



## 5.2. How do the four different measures of adherence correlate with each other?

Figure 5.1 below illustrates a matrix of scatter plots of the various adherence measures plotted against each other. If they tended to agree, one would expect a clustering of points to fall on the 45-degree line.

**Figure 5.1: Correlation Matrix of scatter plots for four measures of adherence**




**Note:** Cumulative rates are plotted for each measure for each observation.

**Abbreviations** used in Fig 5.1: pharm= pharmacy refill; med= medicine measure; clin=clinic visits; sradh= caregiver self-report.

It is clear from these plots as well as from the matrix below (Figure 5.1 and Table 5.1 below) that these different measures do not exhibit a high degree of agreement. However, these comments must be viewed in light of the fact that there was not much variability in these measures. The clustering of straight lines in the plot indicates the many observations with measures of 100% or close to 100% (indicated by 1's).

**Table 5.1: Correlation Matrix of Measures (unadjusted)**

| Variable | Pharmacy Rho ( Prob > \|t\|) | Medicine measure Rho ( Prob > \|t\|) | Clinic visits Rho ( Prob > \|t\|) | *CG self-report Rho ( Prob > \|t\|)* |
|---|---|---|---|---|
| **Pharmacy Refill** | 1.000 | | | |
| **Medicine measure/pill count** | -0.13 (0.22) | 1.000 | | |
| **Clinic visits** | 0.35 (0.000) | -0.21 (0.04) | 1.000 | |
| **Care Giver Self-report** | 0.04 (0.65) | 0.09 (0.38) | 0.09 (0.32) | 1.000 |

Using Spearman's correlation matrix (data was skewed, thus the assumption of normality is violated), the measures in agreement were pharmacy refill (pharm) and clinic visits (clin) (r=0.35; p=0.000). One would expect this result since patients attend clinic on the day that they collect their ARVs from the pharmacy, especially during the first 6 months after initiation of ARVs, thereafter, clinic visits would be scheduled more infrequently than pharmacy refill visits. Clinic visits was significantly yet negatively correlated with Medicine measure/pill counts (r= -0.21; p=0.04) indicating that those with higher adherence rates by clinic visit had lower adherence rates by medicine measure. There was no association between caregiver self-reported adherence and any other measure. Even for the correlations found, the sizes of the correlations are small.



## 5.3. How do the measures correlate with viral load at 6 months?

Since there is no 'gold standard' adherence measure, virological outcome was used to determine the validity of the four measures as explained in chapter 3. Justification for use of viral load as the reference measure was that this was a treatment naïve population followed up from initiation of ARV therapy for 6 months. No children exposed to NVP during PMTCT had NVP in their treatment regimens. Thus, lowering the possibility that virological failure would result from resistance, rather than any other factor such as pharmacokinetic properties or non-adherence.

### 5.3.1. Unadjusted Correlations of measures with Viral load

Firstly, unadjusted correlation analyses of measures with 6 month viral load were conducted. The results of these analyses are in Table 5.2 below:

**Table 5.2: Correlations of 6 month viral load with adherence measures**

| ***Variable*** | *Log viral load 6 (Prob > F; p value)* |
|---|---|
| **Logvl 6** | **1.0000** |
| **Pharmacy refill** | **-0.17** (0.07; p=0.16) |
| **Medicine meas.** | 0.04 (0.69; p= 0.69) |
| **Clinic visits** | -0.15 (0.19; p= 0.20) |
| **Caregiver Self-report** | **-0.21** (0.16; p=0.16) |

The measure with the strongest inverse association with 6 month viral load was caregiver self-reported adherence (r=-0.21), followed by pharmacy refill measure (r=-0.17) and clinic visits (r=-0.15). However, regression analyses conducted to determine the significance of these unadjusted associations showed that none of the measures had significant associations with viral load at 6 months (Table 5.2).

### 5.3.2. Correlations of measures with 6 month viral load (Adjusted for baseline viral load)

There was an inverse association between baseline viral load and pharmacy refill (r=-0.17) and a positive association with medicine measure (r=0.12). However, these associations were weak. Baseline viral load was therefore used as the covariate in subsequent analyses.

Analyses, adjusted for baseline viral load, were conducted to determine correlation of measures with 6-month viral load (see Table 5.3). To test association with log viral load at 6 months, models with the logged viral load at baseline only as well as models

with logged viral load at baseline plus each of the adherence measures were fitted. Logged baseline viral load was significant in all these models (p<0.001).

**Table 5.3: Spearman's Correlation of measures with 6 month viral load**

| Variable | Log vload (6)<br>(Prob > F; pvalue) |
|---|---|
| Log viral load (6 months) | 1.000 |
| Log baseline viral load | 0.35<br>P < 0.001 |
| Pharmacy refill | -0.17<br>(0.000; p=0.18) |
| Medicine measure | 0.04<br>(0.005; p=0.76) |
| Clinic visits | -0.15<br>(0.000; p=0.23) |
| Caregiver Self-report | -0.21<br>(0.000; p=0.12) |

*adjusted for baseline viral load

For the adherence measures, there was no difference in values between adjusted (for baseline viral load) and unadjusted models in respect of correlation with 6 month viral load. None of these associations were statistically significant.

## 5.4. Exploring associations between VL outcome and potential confounders

Because disease severity may confound a relationship between adherence and viral load outcome, the variables indicating disease severity, hypothesized to influence viral load (Table 5.4) were tested for association before a more extensive model was fitted to determine the correlation of measures with viral load outcome at 6 months.

**Table 5.4: Potential confounding variables for Viral Load outcome**

| Variable | Hypothesis Statement |
|---|---|
| Recent sickness | Illness may result in higher viral loads due to immune suppression. |
| Health problem | As above |
| Current TB disease | As above |
| WHO staging | Those in stages 3 and 4 may have severe immune suppression and therefore higher viral loads. |
| Recent Hospitalization | As for "sickness", "health problems"; "TB" and "WHO Staging" above |
| "other drugs" | These drugs may include drugs for chronic conditions which may influence immune strength and thus viral load. |
| Baseline viral load | A higher viral load at baseline may influence the viral load outcome at 6 months i.e. if it is very high; the decline at 6 months may be dramatically reduced but not undetectable. |
| Baseline height-for-weight z-score | Lower z-scores may indicate severe immune suppression thus higher viral loads |
| Baseline weight-for-age z-score (WAZ) | As above |
| Baseline height-for-age z-score (HAZ) | As above |



A series of chi-square tests were used to explore the relationships between the categorical potential confounders (Table 5.5). The objective was to identify which confounders to include in a multivariate analysis taking account of co-linearity of confounders. As expected, there was a strong association found between recent sickness and recent hospitalization ($p<0.000$), between recent sickness and other drugs ($p=0.03$), and between recent sickness and WHO staging of HIV disease ($p=0.03$).

A strong association was found between recent hospitalization and health problems ($p=0.001$), between recent hospitalization and other drugs ($p<0.001$), and between recent hospitalization and WHO stage ($p=0.004$). Lastly, significant associations were also detected between current TB and other drugs ($p<0.000$) and WAZ and 'health problem' ($p=0.02$).

**Table 5.5: $\chi^2$ statistics for disease severity**

| Variables | | (N=135) $\chi^2$ | P value |
|---|---|---|---|
| Recent Sickness | Health Problem | 3.27 | 0.07 |
| Recent Sickness | TB | 0.27 | 0.63 |
| Recent Sickness | WHO stage | 8.96 | 0.03 ** |
| Recent Sickness | Recent hospitalization | 40.60 | 0.000 ** |
| Recent Sickness | Other drugs | 5.07 | 0.03 ** |
| Health Problem | TB | 1.52 | 0.22 |
| Health Problem | WHO stage | 3.52 | 0.06 |
| Health Problem | Recent hospitalization | 11.78 | 0.001 ** |
| Health Problem | Other drugs | 0.91 | 0.34 |
| TB | WHO stage | 0.82 | 0.36 |
| TB | Recent hospitalization | 1.08 | 0.30 |
| TB | Other drugs | 31.57 | 0.000 ** |
| WHO stage | Recent Hospitalization | 9.47 | 0.002 ** |
| WHO stage | Other drugs | 0.35 | 0.55 |
| Recent hospitalization | Other drugs | 8.25 | 0.004 ** |
| Weight-for-age z-score(WAZ) | Health Problem | 5.73 | 0.02** |
| Height-for-age z-score(HAZ) | Health Problem | 2.11 | 0.15 |
| Weight-for-height z-score(WHZ) | Health Problem | 2.17 | 0.14 |

All with 1 degree of freedom except for those tests involving WHO stage* that had 2 df' (*dichotomized into 1&2 | 3&4)
** indicating statistically significant association



The relationship between each of the potential confounder variables were tested for association with baseline viral load using box plots and Kruskal Wallis tests and none were found to be significantly associated (Appendix 14). These results allowed the use of baseline viral load as a control without concern about co-linearity. However, since several of the severities of illness variables were associated with each other, caution was exercised in subsequent modelling. 'Recent sickness' was not used in the same model as 'recent hospitalization', 'other drugs', 'current TB' or 'WHO staging'. 'Other drugs' was not used in a model with 'recent hospitalization', nor was 'recent hospitalization' used in the same model as 'WHO staging'. 'Health problem' was not used in a model with 'WAZ scores'.

### 5.4.1. Association between potential confounders and 6 month viral load

The relationship between categorical potential confounder variables and viral load at 6 months were examined using box plots (Appendix 14) and Kruskal Wallis tests. Kruskal Wallis tests found evidence of a difference in median logged viral load by 'health problems' (p=0.003; $\chi^2$ = 8.49 with 1 degree of freedom). Thus, children whose caregivers reported that they were experiencing a health problem at initiation of ARVs, differed in their log median viral load at 6 months from those who did not.

Baseline height-for-age (HAZ), weight-for-age (WAZ) z-scores and reporting a health problem at ARV initiation, were significantly associated with viral load outcome (p=0.02, 0.02, 0.03, respectively). Those reporting a health problem were 0.39 as likely as those who did not, of achieving virological suppression, thereby confirming the results of the Kruskal Wallis tests reported in the paragraph above (Table 5.6).

**Table 5.6: Disease Severity Variables – Association with viral load suppression**

| Disease Severity Variable | Odds Ratio | SE | Z | P > \|Z\| | 95% CI |
|---|---|---|---|---|---|
| WHZ | 1.29 | .21 | 1.55 | 0.12 | 0.94 ;1.77 |
| HAZ | 1.34 | .17 | 2.33 | 0.02 | 1.05 ;1.72 |
| WAZ | 1.43 | .21 | 2.42 | 0.02 | 1.07 ;1.90 |
| Health problem | 0.39 | .17 | -2.18 | 0.03 | 0.17 ;0.91 |
| Recent sick | 0.88 | .39 | -0.29 | 0.77 | 0.37 ;2.09 |
| Recent hospitalization | 0.87 | .39 | -0.32 | 0.75 | 0.36 ;2.11 |
| Current TB | 1.01 | .47 | 0.02 | 0.98 | 0.41 ;2.50 |
| WHO staging (3&4) | 0.94 | .43 | -0.14 | 0.89 | 0.38 ;2.31 |



## 5.5. Correlation of measures with viral load adjusted for disease severity

In order to test the strength of association between adherence measures and 6 month log viral load, proxies for severity of illness found to be significantly associated with viral load were added to the model, starting with 'health problems'. Regression analysis resulted in significant association between viral load at 6 months and HAZ and WAZ scores (p=0.02, 0.02, respectively).

Each adherence measure was fitted in a model that included log baseline viral load and 'health problems' as predictors of viral load outcome. A significant association between caregiver self-report and 6 month viral load outcome was established in this model (p=0.03), illustrated in Table 5.7. Thus, results indicate that a high adherence score using caregiver self-report is likely to result in a low viral load. This was the only significant association between adherence measure and viral load at 6 months adjusted for disease severity (indicated by 'health problem'). Including more than two control variables did not improve the models and thus the adjusted model in Table 5.7 was chosen to best illustrate the association between log viral load and the adherence measures.

**Table 5.7: Association of measures with viral load suppression (adjusted model 1)**

| Log viral load | Measure β | Measure Std. Err | Measure t-value | Measure P>\|t\| | Measure 95% CI Interval | |
|---|---|---|---|---|---|---|
| Caregiver self-report | -2.37 | 1.05 | -2.26 | 0.03 | -4.46 | -0.29 |
| Pharmacy refill | -1.00 | 0.65 | -1.54 | 0.13 | -2.28 | 0.29 |
| Clinic visits | -0.81 | 0.62 | -1.31 | 0.19 | -2.04 | 0.42 |
| Medicine measure | 0.01 | 0.57 | 0.01 | 0.99 | -1.13 | 1.14 |

*This model includes log baseline viral load and 'health problems' as control variables.

To further illustrate the ability of each measure to predict virological outcome, the proportion of adherent patients with virological suppression was calculated for each measure, using a ≥95% cut off to indicate good adherence (Table 5.8)

**Table 5.8: Proportion adherent among those with undetectable Viral Load**

| Measure | N | Frequency with undetectable viral load <400 copies per ml | Proportion adherent* among those with undetectable 6 m viral load |
|---|---|---|---|
| **Caregiver self-report** | 113 | 70 (61.95%) | 65/70 (92.85% ) |
| **Pharmacy refill** | 116 | 73 (62.93%) | 44/73 (60.27%) |
| **Clinic visits** | 116 | 73 (62.93%) | 54/73 (73.97%) |
| **Medicine measure** | 87 | 55 (63.21%) | 43/55 (87.27%) |

* using ≥95% cut-off for each adherence measure

The majority (93%) of those with undetectable viral loads had ≥95% adherence according to caregiver self-reported adherence measure. However, pharmacy refill measures and clinic visits measures did not yield this high percentage of adherent patients among those with undetectable viral loads but medicine measure identified

87% of those with undetectable viral loads at ≥95% adherence. However, half of the medicine measures were over 100% adherence with a mean adherence rate of 115% for those with more than 100% adherence according to medicine measure. This implies that medicine measure would have low sensitivity (section 5.6).

There was a lack of variance in the data amongst the four adherence measures. On closer examination of the data, residuals were approximately normal and there did not appear to be non-constant variance. Examining the large residuals showed that these were mostly cases for which the model underestimated the viral load i.e. the model did not have sufficient information to explain why those people had such high viral load outcomes. The discernable line in the plot of fitted values vs. residuals corresponds to a group of patients who all had a value for 6 month viral load of 50 (number used in data for undetectable viral load). The model consistently over predicts 6-month viral load values for this group. Note that most of these patients also had a value of one (100%) for their caregiver self reports and there was little variability to differentiate between cases in a meaningful way. Thus, the interpretation of this data is that those with undetectable viral loads (<50 copies per ml, in this instance), were those who also had 100% adherence according to caregiver self-report.

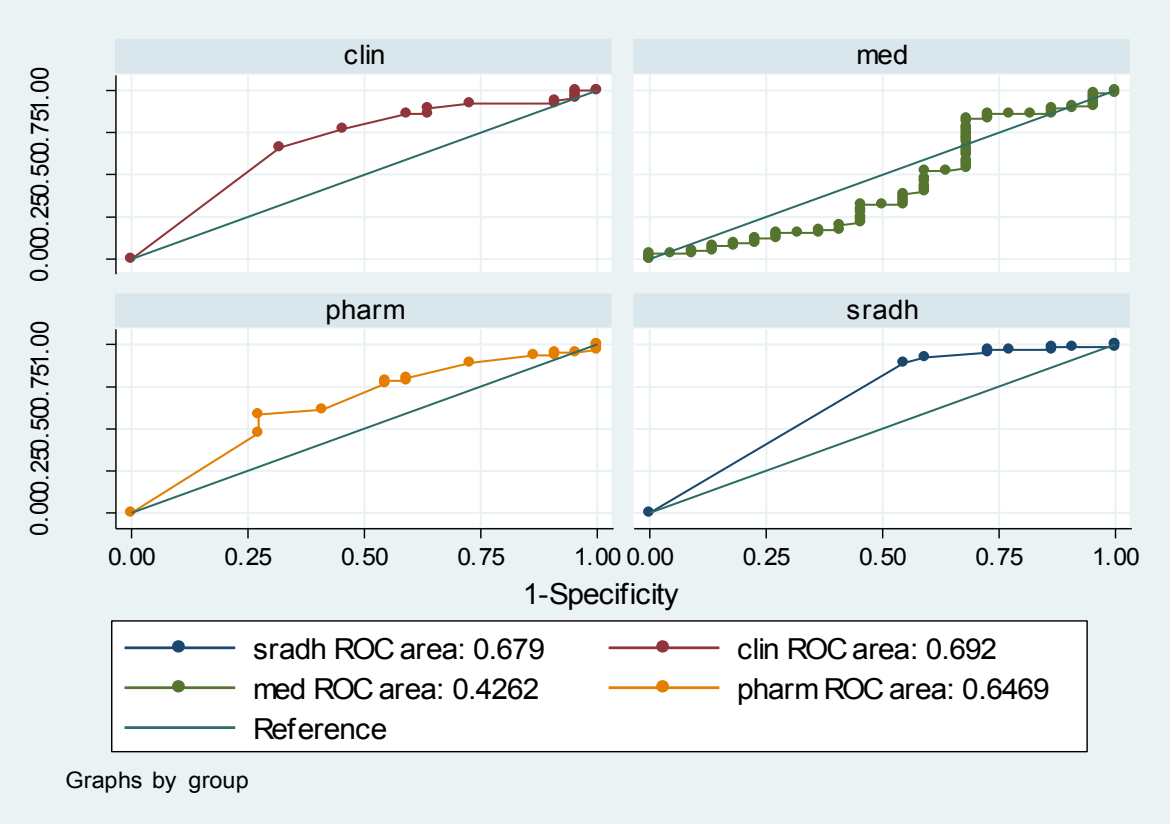
In conclusion, using logistic regression modelling, the best agreement was between caregiver self-report and viral load at 6 months when adjusted for baseline viral load and disease severity.



## 5.6. Sensitivity & Specificity of Adherence Measures

Sensitivity and specificity analyses further tested the ability of the adherence measures to identify the 'true' adherent and non-adherent patients given various thresholds in reference to viral load. Receiver Operator Curves (ROC) were used to illustrate of the 'best' measure'. In this instance, viral load at 6 months was dichotomized into <400 copies per ml (1= suppressed) and >400 copies per ml (0= unsuppressed).

**Figure 5.2: Receiver Operator Curve for Four Adherence measures**




*Analysis using undetectable (< 400 copies per ml) 6 month viral load as reference.

Figure 5.2 illustrates that caregiver self-report (sradh) is a slightly better method for identifying the adherent patients with the most values to the top left of the curve (area under the curve = 0.68 vs. pharmacy refill (0.65) and medicine measure (0.43). Medicine measure differed significantly from the other measures ($\chi^2$= 6.66 with 1 degree of freedom; p= 0.01). There was only a 0.01 difference in values of the area under the curve, between caregiver self-report and clinic visits (0.68 vs. 0.69) however; the shape of the curve indicates better sensitivity for caregiver self-report than clinic visits.

**Table 5.9: Sensitivity and Specificity of adherence measures at 95% threshold**

| Adherence Measure | | % | Correctly classified % | Area under the curve | 95% CI |
|---|---|---|---|---|---|
| **Caregiver self-report** | Sensitivity | 93.98 | 76.99 | 0.63 | 0.54 ;0.72 |
| | Specificity | 30.00 | | | |
| **Pharmacy refill** | Sensitivity | 61.63 | 63.79 | 0.65 | 0.53 ;0.77 |
| | Specificity | 70.00 | | | |
| **Clinic visits** | Sensitivity | 74.42 | 68.97 | 0.66 | 0.55 ;0.77 |
| | Specificity | 53.33 | | | |
| **Medicine Measure** | Sensitivity | 24.62 | 32.18 | 0.43 | 0.27 ;0.58 |
| | Specificity | 54.55 | | | |

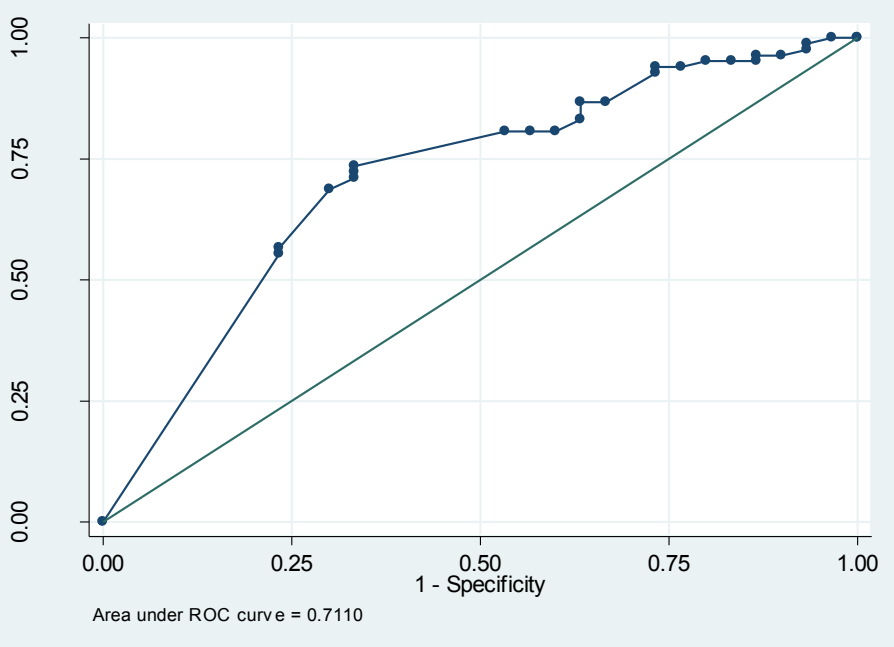
The generally accepted threshold for adherence to HAART is 95%. Table 5.9 illustrates the sensitivity and specificity of each adherence measure at the 95% threshold. Caregiver self-report has the highest sensitivity and highest predictive value (77%), to detect adherence but has the lowest specificity (to detect the true non-adherence) compared with pharmacy refill, clinic visits and medicine measure. Clinic visits had the second highest sensitivity value with the second highest predictive value to detect adherence and higher specificity than caregiver self-report did.

## 5.7. A composite measure of adherence?

A composite measure of adherence was modelled by combining caregiver self-report and clinic visit due to these two measures having the best predictive ability amongst the four measures (Figure 5.3). This composite measure resulted in a larger value for the area under the curve (0.71) than either caregiver self-report (0.63) or clinic visits (0.66). This composite measure was significantly associated ($p < 0.000$) with viral load (OR=5.22 CI: 2.12; 12.8)

However, this composite measure did not increase sensitivity, specificity or the predictive value more than any of the individual measures, though it increased specificity substantially more than caregiver self-report on its own; but the sensitivity, specificity and predictive values were similar to those for pharmacy refill, namely, ('Sensitivity': 68.67% ;'Specificity': 70.00% and 'Correctly classified': 69.03%).

**Figure 5.3: Receiver Operator Curve for Composite Measure**




Using logistic regression modelling, the odds of virological suppression given adherence was analyzed for each measure including three different disease severity variables in the three models in combination with baseline viral load (Table 5.10). Adherence, as measured by caregiver self-report and clinic visits were more likely to predict virological suppression. These findings were significant for models 1, 2 and 3 (for caregiver self-report p= 0.002, 0.003 and 0.001, respectively) and for clinic visits (p= 0.01, 0.01, 0.02, respectively.)

**Table 5. 10: Odds of virological suppression given adherence (>95%) for four measures**

| Model 1 (baseline viral load, health problem and HAZ) | | | | | |
|---|---|---|---|---|---|
| | **Odds Ratio** | **SE** | **z** | **P>\|z\|** | **95% CI** |
| Caregiver self report | 6.03 | 3.45 | 3.14 | 0.002 | 1.97 ;18.48 |
| Pharmacy refill | 1.83 | 0.85 | 1.30 | 0.19 | 0.74 ;4.56 |
| Clinic visits | 3.22 | 1.48 | 2.54 | 0.01 | 1.30 ;7.94 |
| Medicine Measures | 1.55 | 0.83 | 0.83 | 0.41 | .55 ;4.41 |
| | | | | | |
| **Model 2 (baseline viral load, health problem and WAZ)** | | | | | |
| | **Odds Ratio** | **SE** | **z** | **P>\|z\|** | **95% CI** |
| Caregiver self report | 5.67 | 3.27 | 3.01 | 0.003 | 1.83 ;17.57 |
| Pharmacy refill | 1.93 | 0.89 | 1.41 | 0.16 | .78 ;4.78 |
| Clinic visits | 3.18 | 1.46 | 2.52 | 0.01 | 1.29 ;7.82 |
| Medicine Measures | 1.60 | 0.86 | 0.87 | 0.38 | 0.56 ;4.59 |
| | | | | | |
| **Model 3 (baseline viral load and health problem)** | | | | | |
| | **Odds Ratio** | **SE** | **z** | **P>\|z\|** | **95% CI** |
| Caregiver self report | 6.52 | 3.81 | 3.20 | 0.001 | 2.10 ;20.53 |
| Pharmacy refill | 2.44 | 1.16 | 1.88 | 0.06 | 0.96 ;6.19 |
| Clinic visits | 3.04 | 1.38 | 2.44 | 0.02 | 1.25 ;7.40 |
| Medicine Measures | 1.28 | 0.67 | 0.47 | 0.64 | 0.46 ;3.55 |



In conclusion, caregivers self-report is associated with virological suppression when controlling for disease severity and baseline viral load. However, adherence (>95%) measured by caregiver self-report and clinic visits, provide the most significant odds of virological suppression. Implementing these measures in a routine clinic setting is feasible. Since caregiver self-report is significantly associated with viral load outcome at six months it was used as the adherence measure in subsequent analyses to identify correlates of adherence.

# CHAPTER 6
# RESULTS PART 3: FACTORS INFLUENCING ADHERENCE

## 6.1. Introduction

Exploratory analysis was conducted to determine the effect of several variables on adherence.

Caregiver self report was used as the measure of adherence in the analysis of factors influencing adherence since this method of adherence measurement was more closely associated with virological success than any other measures (see Chapter 5).

A conceptual framework based on the hypotheses of the possible relationships between risk factors and adherence was developed. The conceptual framework included four domains, namely, child characteristics, caregiver characteristics, Socio-economic characteristics and health system characteristics (Appendix 8). This framework guided the choice of variables entered into the models.

It should be borne in mind that the mean cumulative rate of adherence according to caregiver self-report was 85.38%. This means that the majority of the cohort were adherent. This resulted in extremely little variability in the data and thus the ability to detect significant differences between the adherent and non-adherent groups was unlikely, given the sample size.

Exploratory data analysis was conducted using bivariate and stepwise regression modelling. The stepwise models provided different results indicating that the models were unstable and that the study was possibly underpowered to due to a lack of variance in the data. Despite these limitations, the results indicated a trend in data that is in keeping with other adherence studies including some surprising results.

## 6.2. Characterization of cohort by adherence status

The variables which characterized the cohort were analyzed in relation to adherence status, based on caregiver self-reported adherence with ≥95% used as the cut-off for adherence (see Table 6.1). The mean adherence rate amongst the non-adherent patients was 81, 5% vs. 100% for the adherent.

A logistic regression model was fitted for each of the hypothesized variables in relation to adherence. These marginal models revealed that four variables, namely, 'Any other', 'grants', 'counsel'[50] and depression were significant risk factors for adherence. First, caregivers who reported to have received counselling by counsellors at initiation of their child's ARVs, were 3.2 times more likely to be adherent (OR= 3.2, P=0.03) than those counselled by a doctor or a nurse. ; Second, having another person in the household, other than the index child, infected with HIV (OR = 0.34, p=0.05) resulted in these caregivers being 0.34 times less likely to be adherent than those who did not report any other HIV infected individual in the household (p=0.05). These two variables were highly significantly associated with each other (p=0.004) where a person with another infected family member was less likely to be counselled by a counsellor (70% vs. 45%).

Third, those who received grants were 2.71 times more likely to be adherent than those who did not. Fourth, children who had caregivers with scores indicating depression at baseline were 0.07 times less likely to be adherent than those who did not (p=0.01). "Counsel" and "depression" were significantly associated with each other, where a person who was depressed at baseline, was 0.28 times less likely to have been counselled by a counsellor for initiation of ARVs (p=0.001).

An interesting observation is that a higher proportion of non-adherent patients reported undergoing significant life events compared to the adherent group, though these results were not statistically significant. These 'significant life events' were defined as funerals, illness of primary caregiver, illness of another household member other than the index patient, illness of sibling, hospitalizations and retrenchments. An

[50] Definitions of variables were given in Chapter 3: Table 3.5.

open-ended section to the question solicited 'other' events not specified. These were reported as 'moving house' and 'having another baby'.

The results regarding PMTCT participation deserves comment despite results not being statistically significant. Fewer children in the adherent group belonged to mothers who participated in the PMTCT programme. On closer examination, results showed that 67% of children whose caregivers did not participate in PMTCT were younger than 13 months of age with a mean age of 7.5 months. The unadjusted odds ratio for age less than 13 months and participation in PMTCT was 1.73 but this was not significant (p=0.17). Closer examination of the data, using Kruskal Wallis tests, indicated that the ages of children whose biological parents participated in the PMTCT programme differed from those who did not. This difference was statistically significant with younger (<27 months of age) children's biological mothers more likely to have participated in the PMTCT programme than older children ($\chi^2$=8.02; p=0.0046). It should be borne in mind that the PMTCT programme commenced in May 2004 and study enrolment commenced in October 2004, thus non-participation may have been due to a lack of access to services rather than conscious choices on the part of biological mothers.

**Table 6.1: Characterization of Cohort by adherence status**

| | Variable | Adherent (≥95%) N=111[1] | Non-Adherent (<95%) N=19* | OR (95% CI) | p-value (0.05) |
|---|---|---|---|---|---|
| | | **Mean (SE)** | **Mean (SE)** | | |
| **Child Characteristics** | Age (months) | 26.78 (2.26) | 25.45 (4.75) | 1.00 (0.98;1.02) | 0.81 |
| | Gender (M) | 0.54 (0.05) | 0.68 (0.11) | 0.54(0.19;1.53) | 0.25 |
| | Recent illness | 0.37 (0.05) | 0.21 (0.10) | 2.19 (0.68; 7.06) | 0.19 |
| | last hospitalization (months) | 6.20 (1.32) | 4.72 (1.65) | 1.01 (0.96 ;1.06) | 0.64 |
| | Otherdrugs (Y) | 0.54 (0.05) | 0.58 (0.12) | 0.85 (0.31 ;2.28) | 0.75 |
| | WHO stage 3&4 | 0.71 (0.04) | 0.74 (0.10) | 0.88 (0.29 ;2.60) | 0.82 |
| | IDC attend (Yes) | 0.76 (0.04) | 0.74 (0.10) | .99 (0.99 ; 1.00) | 0.19 |
| | Since (months) | 8.88 (1.33) | 13.65 (3.95) | 0.98 (0.96; 1.01) | 0.20 |
| | Current TB (Yes) | 0.27 (0.04) | 0.37 (0.11) | 0.63 (0.22 ;1.76) | 0.38 |
| | Health Problem (Yes) | 0.42 (0.05) | 0.42 (0.12) | 1.01 (0.37 ; 2.70) | 0.98 |
| **Caregiver Characteristics** | Biological Parent (Y) | 0.85 (0.03) | 0.89 (0.07) | 0.65 (0.13 ; 3.07) | 0.58 |
| | PMTCT (Yes)[2] | 0.36 (0.05) | 0.53 (0.12) | 0.51 (0.19 ;1.35) | 0.17 |
| | age (20-30yrs) | 0.60 (0.05) | 0.68 (0.11) | 0.70(0.24 ;1.98) | 0.51 |
| | Education (Std 10) | 0.29 (0.04) | 0.37 (0.11) | 0.69 (0.25 ;1.92) | 0.48 |
| | Post school educ (Yes) | 0.16 (0.04) | 0.21 (0.10) | 0.72 (0.21 ;2.44) | 0.60 |
| | Unemployed (Yes) | 0.77 (0.04) | 0.63 (0.11) | 1.91 (0.68 ;5.34) | 0.22 |
| | Planning more children | 0.22 (0.04) | 0.32 (0.11) | 0.60 (0.20 ;1.74) | 0.34 |
| | Day care (Bio mother) | 0.86 (0.03) | 0.07 (0.32) | 0.70 (0.14 ;3.31) | 0.65 |
| | Depression | 0.55 (0.05) | 0.95 (0.05) | 0.07 (0.01; 0.53) | 0.01* |
| **Socio-economic Characteristics** | Housing (informal) | 0.52 (0.05) | 0.68 (0.11) | 0.50 (0.18 ;1.42) | 0.19 |
| | Sanitation (inside) | 0.34 (0.05) | 0.26 (0.10) | 1.45 (0.48 ; 4.35) | 0.50 |
| | Water (outside) | 0.58 (0.05) | 0.68 (0.11) | 0.62 (0.22 ;1.17) | 0.38 |
| | Housing density | 4.89 (0.25) | 4.21 (0.53) | 1.13 (0.89 ;1.42) | 0.29 |
| | Any other infected (Yes) | 0.49 (0.05) | 0.74 (0.10) | 0.34 (0.11 ;1.00) | 0.05* |
| | Grants (Y) | 0.61(0.05) | 0.37 (0.11) | 2.71 (0.99; 7.42) | 0.05* |
| | Significant Life events (Y) | 0.45 (0.06) | 0.63 (0.11) | 0.49 (0.17; 1.37) | 0.17 |
| **Health service characteristics** | Access to ARV clinic (ward) | 0.56 (0.05) | 0.47 (0.12) | 1.41 (0.53 ;3.73) | 0.49 |
| | Counselled (by counsellor) | 0.59 (0.05) | 0.32 (0.11) | 3.17 (1.12 ; 8.98) | 0.03* |
| | Referred to IDC for ARVs (Yes) | 0.25 (0.04) | 0.26 (0.10) | 0.94 (0.31 ; 2.85) | 0.92 |

1. The N values are true for 111 and 19 respectively, except where otherwise indicated in the table.
2. The Provincial PMTCT programme commenced in May 2004, prior to this only the Khayelitsha district in the Province, had a programme (since 2001).

### 6.2.1. Characterization of those with missing adherence data

The characteristics of those for whom adherence data[51] was missing (N=5), differed for mean age (40.09 months) with a range of 9.97 to 67.43 months. There was a slight difference in means for the following variables:

(1) There was a mean of 53.20 days since the last hospitalization, compared to 141.74 for non-adherent patients and 186.01 for adherent patients.

(2) The mean number of household members was 5 compared to 4.21 and 4.89 for non-adherent and adherent patients, respectively.

(3) The mean was .40 for caregivers in the age group 20-30 years compared to 0.68 and 0.60 for non-adherent and adherent patients, respectively.

(4) These patients were more likely to have been referred from the wards (0.60) compared to 0.47 and 0.56 for non-adherent and adherent patients, respectively.

(5) Caregivers with standard 10 (Grade 12) education accounted for a mean of 0.20 among this group, compared with 0.37 and 0.29 for the non-adherent and adherent patients, respectively.

(6) The mean for having another person in the household infected with HIV apart from the index child was 0.20 among this group compared to 0.74 and 0.49 for non-adherent and adherent patients, respectively.

(7) Only one caregiver had access to a social welfare grant.

Since this group constitutes a very small sample, the impact of this missing data is not anticipated to be significant enough to have changed the results of the study significantly, had the data not been missing.

## 6.3. Multivariate Logistic regression models

In an effort to evaluate whether there were any other variables (other than those identified in the bivariate analyses) which were significant, multivariate analysis was conducted using forward and backward stepwise models (see Appendix 15). This approach was used to deal with any possible confounding. Models tested included 22

[51] Adherence data refers to caregiver self-reported adherence measures only.

to 27 variables. The 'best' model was one, which included 25 variables (see caption below table 6.2).

In this model (Table 6.2) attendance at the IDC clinic prior to ARV initiation was statistically significantly associated with adherence (p=0.002) with those who attended prior to ARV initiation for HIV management being 59.34 times more likely to be adherent than those who were referred directly for ARVs, however the confidence interval was very wide (4.61;763.53). Except for 'planmore' which entered the model at p=0.07; nine variables entered the model at p<0.05. Those who reported sickness within one month prior to ARV initiation (recent sick), were 18.54 times more likely to be adherent than those who did not (p=0.01). Those counselled by counsellors were 6.24 times more likely to be adherent than those counselled by doctors and nurses at ARV initiation. An interesting result related to fertility plans with those planning to have more children being less likely to be adherent (OR=0.20) than those who were not. Furthermore, those with TB at ARV initiation, living in informal housing and caregivers with depression were less likely to be adherent (OR= 0.09; 0.12 and 0.03, respectively).

On the other hand, a forward stepwise model (Table 6.3) run with (pe 0.1) resulted in the variables indicating being counselled by a counsellor (Counsel) and having another person in the household infected with HIV (Any other) entering the models at marginally significant levels (p=0.07 and 0.10, respectively). The different results from the various models indicate data instability due possibility to the lack of power in the study to deal with the number of variables entered into the models.

**Table 6.2: Results of Backwards Stepwise Regression model**

| Adherence | Odds Ratio | Std.Err | P>\|z\| | 95% Confidence interval |
|---|---|---|---|---|
| **Grants** | **4.89** | **3.77** | **0.04** | **1.08; 22.10** |
| **Recent sick** | **18.54** | **21.38** | **0.01** | **1.93; 177.82** |
| **Planmore** | **0.20** | **0.18** | **0.07** | **0.03; 1.14** |
| **Counsel** | **6.24** | **5.46** | **0.04** | **1.12; 34.66** |
| **Since** | **0.99** | **0.00** | **0.02** | **1.00; 1.00** |
| **Health problem** | **0.11** | **0.09** | **0.01** | **0.02; 0.63** |
| **ID attend** | **59.34** | **77.34** | **0.002** | **4.61; 763.53** |
| **Current TB** | **0.09** | **-0.08** | **0.01** | **0.01; 0.57** |
| **Housing (informal)** | **0.12** | **0.11** | **0.02** | **0.02; 0.73** |
| **Depressed** | **0.03** | **0.05** | **0.03** | **0.00; 0.74** |

**Variables included in the above model** (pr=0.1): agemo recentsick dayslasthosp Otherdrugs since housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender HealthProb IDattend CurrentTB SigLE Grants depressd (see chapter 3 Table 3.5 for description of variables). 25 variables entered into this model (N=86)

**Table 6.3: Results of Forwards stepwise regression model**

| Adherence | Odds Ratio | Std.Err | P>\|z\| | 95% CI |
|---|---|---|---|---|
| **Counsel** | **2.70** | **1.48** | **0.07** | **0.92;7.91** |
| **Anyother** | **0.39** | **0.22** | **0.10** | **0.13; 1.18** |

**Variables included in the above model**: (N=119) agemo recentsick dayslasthosp Otherdrugs since housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender HealthProb IDattend CurrentTB, pe (0.1)

## 6.4. Power Analysis

A power analysis for the predictor variables was conducted to determine what level of power was in the study for each of the variables entered into the models. The results outlined in Table 6.4 indicate that in general, the study was underpowered and thus Type 11 errors[52] were likely to occur in the results. Power ranged from as low as 3% for 'duration of time between hospitalization and ARV initiation (last hospitalization) to 88% for IDC attendance prior to ARV initiation.

Also note that while the sample size varied slightly in the study data, consistent values of N=100 were used to calculate Power. Table 6.4 illustrates the probability of detecting significance if the hypothesized OR was true. It should be noted that the 'hypothetical' odds ratios in Table 6.4 are approximated from the odds ratios found in

[52] A type 11 error occurs when the data is unable to find a difference that exists as opposed to a Type 1 error which results in finding a difference that is not there.

this study. The table illustrates that adequate power (>80%) was present to detect significant differences for three variables, namely, IDC attendance prior to ARV initiation, sanitation (inside flush toilets) and access to grants, if the hypothesized odds ratios were true.

The results indicated that if the hypothesized odds ratios were true, the power was substantially weak to determine significant differences between the two groups (adherent and non-adherent). Variables such as 'recent sickness' prior to ARV initiation (3%); no. of days since last hospitalization (3%); duration of IDC attendance prior to ARV initiation, 'since' (4%); access to ARV treatment via the wards (9%); marital status (11%); age (13%); depression and knowing the names of the ARVs (17%) lacked sufficient power.

**Table 6.4: Power Calculations with Alpha set at 0.05 if the OR was true**

| Group | Variable | Odds Ratio | Power |
|---|---|---|---|
| ***Child Characteristics*** | Age | 1.29 | 13% |
| | Gender (M) | 0.55 | 45% |
| | recentsick (Y) | 1.03 | 3% |
| | HealthProb (Y) | 0.01 | 37% |
| | IDattend (Y) | 2.50 | 88% |
| | Since/idc duration (DAYS/months) | 0.01 | 4% |
| | CurrentTB (Y) | 0.66 | 30% |
| | WHO Stage (3&4) | 0.59 | 39% |
| | Last hospitalization (months) | 0.96 | 3% |
| | Otherdrugs (Y) | 0.40 | 62% |
| ***Caregiver Characteristics*** | Reltochild (Bio) | 0.57 | 38% |
| | PMTCT (Y) | 0.40 | 72% |
| | GiverAge (20-30) | 0.83 | 10% |
| | Educ (Std10) | 0.66 | 30% |
| | PostSchool (Y) | 0.07 | 23% |
| | Employment (unemployed) | 1.81 | 62% |
| | Planmore (Y) | 0.57 | 46% |
| | Day care (Biological mom) | 0.64 | 29% |
| | Depression (>9) (Y) | 1.36 | 17% |
| | Know names of ARVs | 1.36 | 17% |
| | Marital status | 1.20 | 11% |
| ***Socio-economic Factors*** | Housing (Informal) | 0.44 | 63% |
| | Water (Outside) | 0.44 | 63% |
| | Sanitation (Inside) | 2.33 | 81% |
| | Housedensity | 2.5 | 74% |
| | Anyother (Y) | 0.63 | 32% |
| | Grants (Y) | 2.55 | 88% |
| | Significant Life Events (Y) | 0.55 | 45% |
| ***Health System Characteristics*** | Counsel (Counsellor) | 1.89 | 64% |
| | Access (Ward) | 0.83 | 9% |
| | Referred (Y) | 0.40 | 77% |

# CHAPTER 7
# DISCUSSION OF STUDY FINDINGS

## 7.1. Introduction

This chapter provides a synthesis of the main, including important though not significant findings of the study presented in chapters 4 to 6 situated in the context of previous research, where possible. An attempt was made to focus on those studies that are most comparable in terms of study population and methods used, where possible. Finally, limitations of the study will be discussed.

The purpose of this study was three-fold: first, to identify the adherence rate amongst a paediatric population younger than 7 years of age; second, to identify an adherence measure (amongst four) best suited to routine clinic practice within a resource-limited setting and third, to identify correlates of adherence within this setting. No other study on adherence to HAART has previously focussed exclusively on the age group targeted in this study, namely <7 years. The mean age of the cohort was 27 months. The cohort was characterized with severe immune suppression (mean CD4percentage <15%) from households where 76% of caregivers were unemployed and more than half were living in informal dwellings (self-made 'shacks'). The majority of caregivers were the biological mothers of the children.



## 7.2. Adherence Rates and virological suppression amongst the cohort

Paediatric adherence is challenging as is evident from the review in chapter 2. It is estimated that paediatric adherence in general (not HAART specific), is not very high, namely 58% vs. 75% in adults (van Rossum, Fraaij, & de Groot 2002). In contrast, among the cohort of paediatric patients in the present study, 85% had >95% adherence as measured by caregiver self-report with 88% of adherent caregivers reporting no missed doses. This relatively high cohort adherence rate is comparable to other paediatric HAART adherence studies using caregiver self-report measures conducted in resource-limited settings. These include countries such as Uganda, Thailand, South Africa and Nigeria (Nabukeera-Barungi et al. 2007),

(Hansudewechakul et al. 2006; Reddi et al. 2007; Mukhtar-Yola et al. 2006) reporting 89%, 90%, 89% and 80% cohort adherence, respectively.

Seventy-four percent of those for whom six month viral load results were available (N=116), had virological suppression. This finding is markedly better than the results of a paediatric HAART adherence study in Thailand where only 53% of patients were suppressed at 6 months only reaching 76% at 12months (Puthanakit et al. 2005a). It should be noted that the present study was conducted among a treatment naïve population and the follow-up was relatively short (6 months). These factors would mostly preclude treatment resistance[53] from being a major factor in virological failure and thus inferring high adherence from virological suppression would be justified. The fact that virological failure occurred amongst 26% of this treatment naïve cohort should alert our attention. There may be several reasons, as previously alluded to, for virological failure some of which may result from non-adherence and others from pharmacokinetic dynamics. A study conducted at two sites in South Africa (RXH and Baragwaneth Hospital), involving therapeutic drug monitoring of Efavirenz, found that children receiving doses according to the current treatment guidelines were not receiving adequate exposure to the drug (Ren et al. 2007). According to the authors, low Efavirenz concentrations result in rapid emergence of efavirenz-resistant mutations of HIV causing treatment failure. One third of the study cohort had an Efavirenz–based regimen. Efavirenz capsules needed to be opened and dispersed in water for administration in this very young cohort. This practice in itself could lead to under dosing if all the medication is not dissolved and given to the child. However, there is insufficient data in this study to determine the cause of virological failure amongst this group.

Baseline viral load was highly correlated with viral load outcome at six months. Higher baseline values resulted in higher values at six months. This confirmed the hypothesis that if the baseline viral load was very high, the decline after six months may be significant, though detectable. This finding is similar to results of a study among adults on HAART, which found that baseline viral load values were

[53] I acknowledge that there may be resistant strains in circulation in the community which may affect treatment 'naïve' individuals.

significantly associated with virological outcome measured at six months of initiation of treatment[54] (Mathews et al. 2002).

An a priori hypothesis in the present study was that disease severity influences virological outcome. Several indicators for disease severity were used and the indicator which was consistently associated with viral load outcome at 6 months was the variable indicating that the caregiver had reported that the child had a health problem at ARV initiation ("health problem'). Those whose caregivers reported a health problem at ARV initiation were more likely to have virological suppression than those who did not. In a resource-limited setting, this could be a very simple predictor of adherence. The result supports previous findings (cited in chapter 2) that severity of illness and in this case, the caregiver's perception of severity of illness, impacts positively on treatment success as indicated by virological suppression, at least in the short term. Some may argue that the caregiver report of a health problem at ARV initiation is not an objective measure of disease severity but according to the data of the present study, it was a good proxy.

## 7.3. Adherence Monitoring: Comparing the four Measures

In 1998 Flexner noted that it was impossible to measure adherence in an outpatient setting with absolute accuracy and precision and we still face this dilemma in 2008 (Flexner 1998). This study was an attempt to find the 'least flawed method' amongst the 'flawed', which is suitable for ambulatory patients in a resource-poor setting.

The adherence measures displayed high sensitivity (to detect adherence) but not high specificity (to detect non-adherence). The use of composite measures such as combining caregiver self-report and clinic visits were tested to increase specificity. In the present study a composite measure of caregiver self-report and clinic visits yielded higher specificity than either caregiver self-report or clinic visits but caregiver self-report had the highest sensitivity at the $\geq$95% threshold. In the absence of a gold

[54] This cohort study was conducted amongst 888 adult patients followed up for 6 months. I was unable to find evidence in a comparable paediatric HAART adherence study in resource-limited settings in the literature.

standard measure of adherence, viral load suppression was used as the reference measure with acknowledgement of its limitations as outlined in chapter 2.

Among the four measures, the medicine measure/pill count was the most challenging measure to implement. All children in this study had syrup formulations in their regimens (due to their young age). There were large volumes issued and caregivers often neglected to return the bottles for measurement. There were incidences reported of spillage, vomiting and even broken bottles, which led to overestimation of adherence with a mean of 115% adherence for those with over 100% adherence. Those with more than 100% adherence comprised 50% of the group measured by medicine measure. The overuse of medication from the container may not translate into absorption by the child since not even the caregivers were clear about 'how much the child actually got in' after a vomiting or spitting episode. Caregivers try to repeat doses in an attempt to give the 'correct' dose. Amongst very young children (< 1yr) this may be easier than with older children who may fuss and refuse repeat dosing. This measure was not correlated with virological outcome. The adherence data according to medicine measure, clearly illustrates the difficulties in paediatric ARV treatment administration using unpalatable formulations or adapting adult capsules, like opening and dissolving Stavudine and Efavirenz capsules. In addition, three separate formulations have to be administered which triples the problem for the caregiver and the child. These facts indicate that this measure is not practical as an adherence measure in a paediatric population. Davies et al (2007) had similar findings with regard to the adherence rates in excess of 100% as well as finding no association between medicine measure and viral load.

No measures were significantly correlated with virological outcome in unadjusted associations. On the other hand, caregivers self-report was significantly correlated with virological outcome when adjusted for disease severity in this study (p=0.001). However, the odds of virological suppression given adherence, using clinic visits as the measure of adherence, was significant and half that of caregiver self-report (OR=3.2; p=0.02 vs. OR=6.0)

Caregivers self-report, pharmacy refill and clinic visits, as measures of adherence, were the easiest methods to implement in a routine clinic setting. These three

methods have the added value of alerting the clinician to a problem at the first sign of non-adherence such as missing doses (in the case of caregiver self-report) or missing an appointment such as a pharmacy refill date or a clinic appointment.

Several paediatric studies have found correlations between caregiver self-report and viral load and some were in resource-poor settings, namely, Cotê d' Ivoire and Thailand (Gibb et al 2003; Arrivé et.al 2005; Hammami et al, 2004; Marhefka et al. 2006; Puthanakit et al. 2005a).

Possible reasons for the 'good performance' of this measure may be: first, for the duration of the study, doctors and nurses generally did not speak the patient's first language which is predominantly Xhosa, while the research assistant who administered the caregiver self-report questionnaire in this study belonged to the same cultural and language group of the patients. It is hypothesized that the patients were therefore more willing to declare non-adherent behaviour to the research assistant than they would to a doctor or nurse because they were able to communicate comfortably. Farley et al. (2003) suggested that the caregiver self-report performs 'better' when it is administered by someone with whom the patient 'feels comfortable'. In this study, the interviewer was not directly responsible for providing the clinical care and this may have made caregivers feel more willing to declare their adherence problems without fear that it would impact on their child's quality of care. Second, the standard PACTG questionnaire provided a tool for phrasing questions in a non-judgmental way and asking for specific information which has been proven to provide a better picture of how the patient is managing adherence (Chesney et al. 2000b). Finally, this hypothesis is further supported by research which found that using face-to-face interviews for patients' reports and the way in which questions are asked, plays a role in the quality of information received (Ickovics & Meisler 1997).

The lack of high specificity for the adherence measure is not unique to this study. One other study that employed multiple measures in a paediatric adherence study using caregiver self-report, pharmacy refill, clinic appointments, physician adherence assessment and MEMS-monitored medication adherence found that "the highest specificity was attained when both MEMS and pharmacy refill were used in combination" (Farley et al.2003: 217). While the above-mentioned study found a

correlation between viral load at 6 months and clinic appointments as well as physician-assessed adherence, no correlation between caregiver self-report and viral load outcome was found.

The finding that caregiver self-reported adherence was correlated with viral load outcome in this setting is encouraging since it is a 'relatively' low-cost method. Despite the lack of significant agreement between viral load suppression and pharmacy refill and clinic visits, these 'relatively' low cost methods have value in this setting. It may be used to alert the clinician to potential adherence problems at the earliest sign, thereby facilitating timely intervention as opposed to waiting for viral load results which may become available 4 to 6 months later, after the adherence problem has potentially been exacerbated.

The development of improved adherence monitoring techniques, such as the 'Simpill™[55]' technology emerging on the market[56] (a variation on the MEMSCap) may not be appropriate for paediatric adherence monitoring for the reasons outlined in this dissertation regarding syrup formulations as well as costs being prohibitive for routine use among children in resource-poor settings.

## 7.4. Factors impacting on adherence

This study is one of the few paediatric adherence studies in which associations between factors and adherence were statistically derived (Nabukeera-Barungi et al. 2007; Giacomet et al. 2003; Mellins et al. 2004). According to a review of the paediatric adherence literature conducted by (Simoni et al. 2007: 1375):

> "Lists of factors presented are more likely to be derived from clinical experience or surveys in selected areas such as "mental health and coping"; than from theory-driven research or studies in which the associations were examined statistically."

[55] This technology provides 'real-time' adherence monitoring with wireless technology attached to the medication cap

[56] See www.SIMpill.com

This study was exploratory due to the paucity of data regarding paediatric adherence in resource-limited settings at the time of the conceptualization and implementation of the study. As a result, instruments were designed to capture many aspects of the complex dimensions of paediatric adherence based on hypothesis and evidence from paediatric studies primarily in resource-rich settings and the data based on adult HIV infected patients.

### 7.4.1. Child Characteristics

Age of the child was not significantly associated with adherence. This may be due to a unique aspect of the study population which was the young ages of children with access to HAART in a resource-poor setting, with a confined range (<7 years) and the youngest being 3 months old. Published literature generally reported mean ages of between 4 and 12 years with age ranges between 2 and 21 years (3Cs4kids 2008; Nabukeera-Barungi et al. 2007; Mukhtar-Yola et al. 2006; Puthanakit et al. 2005b).

All children in this cohort were of non-school going age and generally all dependent on caregivers to administer their medication. The higher rate of adherence amongst the cohort (85%) may therefore support the findings of studies which report that adherence is higher among younger children (Martin et al. 2007; van Rossum et al. 2002; Arrivé et al. 2005).

No children in this study were told their HIV status because caregivers perceived them to be "too young to know". Thus, the effect of the child's knowledge of their HIV status on their adherence could not be determined.

In bivariate analysis, no child characteristics were associated with viral load. However, in multivariate analyses, children who were ill (p=0.01) and those who had TB (p=0.01) were more likely to be adherent than those who differed on these variables. Attendance and duration of attendance of the IDC outpatient clinic influenced adherence in a contrasting manner. Attendance of IDC prior to initiation of ARVs was significantly associated with adherence in a positive direction (p=0.002). In contrast, the duration of this attendance prior to ARV initiation was

inversely associated with adherence with those in the non-adherent group having a mean of >13 months attendance prior to ARV initiation compared to the adherent group with a mean of <9 months attendance.

A possible explanation for these apparently conflicting results regarding IDC attendance is offered. Caregivers of those who were attending the IDC for a longer time prior to ARV initiation may not have perceived their children as being very ill and the data showed that those who reported 'recent sickness' were more likely to be adherent than those who did not. Clinicians or counsellors may not have provided the same intensity of preparation prior to treatment as those who were referred specifically for ARVs on the assumption that they had sufficient HIV-related knowledge and health care workers may have assumed that these caregivers were comfortable with administering the treatment.

In contrast, children identified and brought into HIV care prior to the initiation of ARV treatment may be at an advantage regarding regular medication administration. Pneumocystis jirovecii pneumonia (PJP) prophylaxis (cotrimoxazole) and multivitamin syrups are standard of care at the IDC. This may create a smoother transition for both caregiver and child, from the administration of these medications to ARVs. However, this is pure speculation and the study was not designed to test these hypotheses.

The health status of the children was associated with adherence. The data showed that children for whom illness episodes during the month prior to initiation of ARVs were reported, as well as children who suffered a 'health problem' at initiation of ARV treatment, were more likely to be adherent than those who did not (p=0.01 each). The younger ages of the cohort and the fact that the study was conducted at the outpatient clinic of a paediatric specialist hospital, indicates that the children were all possibly vertically infected and severely immune compromised.

The mean CD4percentage of <15% and mean log baseline viral load of 5.6 is indicative of the level of severity of illness in this cohort. This statement is supported by the fact that the majority (78.5%) of caregivers perceived the reason for ARV initiation to be "that the child was sick and doctors recommended that the child starts

treatment" and in-patient referral made up 55% of the referrals to the IDC clinic. Similarly, a study in Uganda which found that children who have had at least one hospitalization episode prior to ARV initiation have better adherence and in another study, the PENTA study group found that children with more severe disease have better adherence (Nabukeera-Barungi et al. 2007; Gibb et al. 2003). Thus, the health status of the cohort in general may explain, in part, the relatively high rate of adherence amongst this cohort.

### 7.4.2. Caregiver Characteristics

A high proportion of caregivers were biological mothers (85%) with 61% in the age group 20-30 years. This high rate of biological mothers as primary caregivers of HIV infected children is comparable to a study conducted in Nigeria where 80% of children had a biological mother as their primary caregiver (Mukhtar-Yola et al. 2006). The relatively high rate of adherence amongst this group is in line with an adherence study in India (among non-HIV infected children). This study found that children with biological parents were more adherent (Natu & Daga 2007). Contrary to these findings, a study in Italy found that HIV-infected children in foster care did better (Giacomet et al. 2003).

In bivariate analysis, depression was the only variable which had a statistically significant effect (p=0.01) on adherence with those with depressive symptoms (score >9) less likely to be adherent than those who did not have any symptoms (OR 0.07). The prevalence of depressive symptoms amongst the cohort of caregivers was approximately 18%. A study conducted amongst depressed adult patients on HAART showed that treating depression with anti-depressant medication, improved adherence to HAART (Horberg et al. 2008). This has implications for identification of caregiver symptoms of depression in paediatric ARV treatment programmes if it is inferred that depression treated in the caregiver would impact positively on adherence of the child.

However, this may mean a restructuring of the 'vertical' manner in which ARV services are currently managed in some health care settings in South Africa. To illustrate, identifying caregiver depression in a paediatric treatment facility will mean

that the caregiver will need to be referred to another facility to obtain access to further management and treatment. This may involve spending another day at another facility and may involve further transport costs as well as possibly child-minding arrangements if the mother usually takes care of the child during the day. The evidence from studies show that the caregiver may be more likely to forgo her own (in the case of female caregivers) health care if it impacts on her caring role of the child (Wrubel et al. 2005).

Therefore, while further studies are needed to explore the impact of these caregiver characteristics in a resource-poor setting, the available evidence suggests an appropriate adherence enhancing intervention would involve a family centred model of care. Furthermore, data from the meta-analysis of seven perinatal trials conducted in East, West and South Africa shows that children whose mothers have died have a 3.5-fold higher risk of dying independent of the child's HIV status (Newell, Coovadia, & Cortico-Borja 2004). It is therefore imperative that mother-child dyads be kept intact to ensure adherence and the survival of the children.

There was a trend towards lower mean scores, indicating less depressive or no depressive symptoms, amongst caregivers as treatment duration amongst children increased. Notwithstanding the myriad of factors which impact on caregiver psychological well-being (poverty being a major contributing factor (Brandt 2007)), these results indicate that having a sick child adds to depressive symptoms in caregivers and as children become established on HAART and their health improves, depressive symptoms decrease. This decrease between month 1 and month 6 was not found to be statistically significant in this data but this was probably due to the lack of power to detect a difference on this variable (approximately 17% power in the study[57] and the fact that those with the highest scores at month 1 had missing data at month 6). Depression and stress have been found to impact negatively on adherence among adult patients on treatment (Chesney 2000; Gordilloet al. 1999; Holzemer et.al 1999; Murphy et al. 2001; Patterson et al. 2000). These findings have been confirmed in paediatric adherence studies with higher levels of baseline parenting stress and

[57] See Table 6.4: Power calculations

experiences of negative stressful life events associated with worse adherence as measured by clinic attendance rates (Mellins et al. 2004).

In multivariate analysis (with alpha set at p=0.1) both depression and fertility plans were significantly associated with adherence. Once again those caregivers with depressive symptoms were less likely to be adherent (p=0.03) as well as those caregivers who were planning to have another child (p=0.07). Caregivers who were planning to have another child were 0.2 times as likely to be adherent as those who were not planning to have another child. This finding may be related to the amount of confidence the caregiver had in the child's prognosis.

An interesting finding relates to the knowledge and attitudes of caregivers to ARV treatment in the present study. While the majority expressed the belief that the benefits of ARVs far outweigh the risks, this belief did not translate into hope for a good prognosis. More than half (58%) expressed concern that their child may not live long enough to complete their schooling because of their infection. It should be borne in mind that in the absence of antiretroviral treatment children with HIV-infection are not expected to live beyond their 2$^{nd}$ birthday in resource-poor settings (Newell et al. 2004). It will probably take time for people in this setting to trust that ARVs can increase the life span of children.

It is not known what long-term impact this 'lack of faith' in the ability of ARVs to provide a long life may have on the child's level of adherence. A qualitative study of caregiver perspectives of paediatric adherence found that adherence was affected negatively by children adopting their mother's attitude towards medication (Wrubel et al. 2005).

### 7.4.3. Socio-economic Characteristics

In bivariate analysis, two variables were significantly associated with adherence namely, having another person infected with HIV in the household, other than the index child (p=0.05) and having access to social welfare grants (p=0.05).

Those with another person infected with HIV in the household, other than the index child, were less likely to adhere (0R=0.34) than those without. This factor relates to adherence in several ways.

First, the majority of infected household members (other than infected biological mothers) were fathers, aunts and siblings. This may indicate that children in households where other family members are in need of care and attention are more vulnerable to non-adherence. Often the primary caregiver of the child has multiple care-giving roles, for example, other children (siblings of the index child) who may also be infected as well as partners or other family members. This places an additional burden of care on someone who is also possibly HIV-infected and subject to health constraints.

Second, in the present study very few (10%) caregivers were taking antiretroviral treatment for themselves. The study did not determine how many caregivers were actively seeking health care on a regular basis and thus in need of treatment but not accessing it. Though the implications for caregiver health care appears self-evident, there is a paucity of empirical data to support the assumption that providing a 'family-centred' model of health care will impact positively on the health of the HIV-infected child in particular, as well as the affected child. The results from this study may provide the basis for further research into this factor.

The strong association of access to social welfare in the present study supports the link between adherence and the family context. At the start of this study, the IDC clinic was providing health care and antiretroviral treatment for the caregivers of children on HAART but this programme was halted within three months of the commencement of the study due to health service policy (see Chapter 3).

Social Welfare support was found to impact significantly on adherence with those accessing monthly government grants, almost three times more likely to be adherent as those who did not. This finding should be considered in the context that 76% of caregivers were unemployed and 60% reported receiving some form of social welfare grant. Most (86%) of the grants were childcare dependency grants which was valued at R160 per month during the period of the study. On the surface, the impact of this relatively small amount of income on adherence may not be apparent but may be

explained by the findings from the study by Brandt (2007). Her study among women found that HIV infection and experiencing irregular household income were predictors of depression to an equal extent. She therefore suggested that:

> "…in the case of poverty, the absolute value of household income was less significant than how stable and regular household income was and therefore whether women experienced their households' financial security as predictable." (Brandt 2007: 234)

Thus the impact of grants on adherence may be related to the fact that the majority of the unemployed caregivers had access to at least some form of regular income which ameliorated the depressive symptoms which have been shown to impact on adherence (Chesney 2000). As mentioned above the results of the present study indicate that those caregivers with depressive symptoms were less likely to be[58] adherent than those who did not have depressive symptoms. Similarly, a study among South African AIDS orphans found that AIDS orphans were less likely to have psychological ill health if they lived in a household with access to social security grants, food security and at least one member in employment, suggesting that efforts to alleviate poverty could mitigate the psychological problems manifesting as depression and delinquency in AIDS orphans (Cluver, Gardner, & Operario 2007). This study further illustrates the link between social welfare grants and psychological well-being which was found to influence adherence in the present study

An important though not significant finding, (P=0.17), was that those experiencing "significant life events" were less likely to be adherent (OR=0.49) than those who did not. Experiencing significant life events may be stressful and can cause disruption in daily routine. Furthermore, research indicates that general life stress impacted more profoundly on HIV-infected women (Boland, Moore, & Schuman 1999; Catalan & Burgess 1996; Catz et al. 2000).

In the present study, the most caregivers were biological mothers who were also HIV-infected. There may be several reasons for the association between experiencing a significant life event and non-adherence. For example, attending funerals in this setting often meant that caregivers had to travel long distances to another Province to

[58] To clarify the use of the term adherence in relation to caregivers: I use this reference in relation to the caregiver as a proxy for the child patient since the young ages of these children make them utterly dependent on the caregiver for medication administration.

attend the funeral and often the proceedings would last a number of days causing disruption to daily routine as well as extended periods away from home. One of the reasons often cited for non-adherence in the literature, is 'being away from home' (Chesney 2000). The primary caregiver may leave the young child in the care of someone else for the duration of their travels without disclosing the child's HIV status and thus the importance of administering the medication. Disclosure of the child's HIV status to another person is more important in paediatric ARV treatment than amongst adults. A young child needs someone to act as a secondary caregiver for medication administration in the event that the primary caregiver is unavailable for any reason. In the paediatric context, disclosure of the child's status to others has been linked to adherence to medication (Byrne et al. 2002; Nabukeera-Barungi et al. 2007). On the other hand, the medication may not be easy to administer to a young child by someone who has not been 'taught' how to do it. Syringes are often used in this setting by caregivers to administer the ARV syrups to the young child. The use of syringes to administer medicine may be a 'foreign' concept to those who relate syringes with injections.

While funerals or death in the family was one of the most likely significant life event reported, illness and hospitalizations were often cited as well.

In the multivariate analyses, both the variables 'grants' and 'housing' emerged as statistically significant (p=0.04 and 0.02, respectively). In multivariate analyses, the strength of association between access to grants and adherence became stronger with the odds of adherence being almost 5 times that of those who did not have access to grants.

With regard to 'housing', those in informal housing were less likely (OR=0.12) to be adherent than those who lived in formal (brick built) houses.[59] This finding should be interpreted with caution since the majority of the cohort lived in informal dwellings (76%) and the level of adherence was relatively high for the cohort (85%).

[59] In bivariate analysis housing and adherence were weakly associated but the association was not statistically significant ( OR= 1.13; p=0.29).

### 7.4.4. Health Service Characteristics

The factors explored within this domain related to counselling and access to ARV treatment and service. In bivariate analyses those counselled by a counsellor were 3 times more likely to be adherent (p=0.03). The reason for this finding probably lies in the explanation previously described regarding language and cultural barriers between clinical staff and patients while counsellors (like the research assistant) provide the bridge to close the gap in communication. The lay counsellors employed at the hospital are themselves HIV infected, some of whom are on treatment and others who have children who are on treatment. The counsellors conduct support groups on clinic and as a result are known by the patients and trusted. This improved communication leads to better understanding of the information regarding HIV and antiretroviral treatment as well as dosing instructions in a manner that is culturally sensitive. The counsellor understands the cultural constraints impacting on caregivers' decisions to initiate antiretroviral treatment.

For example, during the first few months of the study, there were patients who did not understand the instructions given by either the doctors or the pharmacist regarding dosing of ARVs and even identification of ARVs from amongst the large volume of medications issued. They would seek out the research assistant (Xhosa speaking) to clarify information. This was during the period when most counsellors were primarily focussing on pre and post HIV test counselling of caregivers with no formal training in paediatric ARV treatment literacy, except as 'experienced' caregivers, though they had received training in adult treatment literacy.[60] Those counsellors who had children on treatment were in a better position to counsel caregivers whose children were about to start treatment.

In the multivariate analyses, adjusted for disease severity, only 'counsel' remained statistically significant in this domain with the strength of association between adherence and 'counsel' increasing to the odds of those counselled by a counsellor

[60] As a result of the researcher's observations, the need for specific training in paediatric treatment literacy was brought to the attention of the clinicians and a programme was subsequently developed by the researcher, together with the clinical team, to train counsellors to counsel caregivers for ARV treatment initiation of their children. This culminated in the development of a 'counselling guide' and a training programme for counsellors which will be rolled out in the Province during 2008.

being 6 times more likely to be adherent than those counselled by either a doctor or a nurse (p=0.04). Thus, the important role of this cadre of 'lay healthcare workers' in this setting, has been demonstrated in this study on paediatric adherence to HAART.

A meta-analysis of 36-controlled studies in chronic disease looking at adherence and long-term health outcomes, found that behaviourally-oriented programs with special attention to patient environments and context, were consistently more successful at improving the clinical course of chronic disease (Mazzuca 1982). Although this research was conducted during the pre-AIDS era these conclusions may still hold true for adherence to HAART. Authors of another study which was a randomized controlled study looking at the efficacy of an adherence enhancing intervention concluded that:

> "Limited evidence suggests that interventions to enhance adherence to antiretroviral therapy in people with HIV are most likely to be successful when they are comprehensive, longitudinal, and tailored to the person" (Tuldra et al. 2000: S154)



While studies cited above involved adult patients on HAART, these are considered relevant in the context of paediatric adherence since adult caregivers are responsible for adherence of their children or children in their care. In the context of paediatric HAART adherence, the data may be interpreted to mean that it is important to prepare caregivers of children about to initiate ARV treatment with the relevant knowledge and skills to ensure good adherence. A strategy to support them throughout the process to cope with the various developmental stages of the child when they will be presented with new challenges to adherence should be in place. One such intervention has been developed and implemented at the IDC (study site) subsequent to the present study (Michaels & Nuttall 2006c).

While the data from the study lacked sufficient variance to clearly 'explain' the reasons for non-adherence amongst the 15% non-adherent patients, given the non-significant findings on the majority socio-demographic variables employed by the study, the following evidence from an intervention study may shed light on this matter. A study using the information, motivation behavioural skills model (IMB) of intervention among Italian adult HIV-infected patients, found that having less than

95% adherence was related to lower levels of behavioural skills, which include self-efficacy, for example, to overcome side-effects and incorporate medication into daily living. Lower behavioural skills were more likely when adherence-related information and motivation were low. Mental health, for example, depression, as well as unstable living conditions and poor access to healthcare all impacted on motivation (Starace et al. 2006). In the present study, depression in the caregiver was more likely to impact negatively on a child's adherence to HAART. Caregivers' levels of self-efficacy and motivation were not determined in this study.

## 7.5. Study Limitations

This study has several potential limitations. First, the study lacked sufficient power to detect significant differences between the adherent and non-adherent groups on most of the variables (see power calculations in Chapter 6: Table 6.4) due in part to the lack of variability in adherence data (high rate of adherence). Several variables, such as the variables used as proxies to indicate disease severity, included due to the exploratory nature of this study, overlapped with each other. Due to the small sample size, many variables available in the database could not be added to the analysis and a hypothesis driven approach was used for variable reduction to approximately 25 variables, which may be considered too many for the small sample. The striking difference between the models in the multivariate analysis illustrated in (chapter 6) suggests data instability. This may be due in part to the lack of variance in adherence, the lack of power related to the sample size to show significant differences for the small effect size as well as missing data on certain variables which caused models to reduce the number of observations to the lowest denominator.

Despite these limitations, the results of the study on factors impacting on adherence indicate a trend in the data which is mostly intuitive including the encouraging finding of the effect of being counselled for ARV initiation by a lay counsellor. The result is considered encouraging because the South African ARV programme is relying increasingly on this cadre of worker in the health care team to facilitate HIV specific information and support on the assumption that this will increase patient retention in ARV programmes.

Second, this study was implemented in a routine clinic setting without additional resources (except an interviewer and the researcher) to create a 'controlled' study environment. This resulted in a higher rate of attrition of subjects than anticipated due to patients being transferred out to other clinics during the study follow-up period and research staff missing patients for interviews and data collection due to return clinic appointments being changed without changes being communicated to research staff, resulting in more missing data than was expected. However, this limitation (conducting a study under 'normal' clinic conditions) can also be seen as strength. The recommendations arising out of the study in a sense have been piloted in the 'real world'.

Third, the study was conducted at a paediatric specialist hospital and though patients were recruited from the outpatient clinic, more than half the patients attending the IDC are referred from the wards. This may have led to the sample being biased towards ill children and as described in the literature and cited above, adherence has been shown to be greater among children who were very ill or hospitalized. However, the study population described in the study is drawn from the same population attending primary care clinics in the Greater Cape Town area.

Fourth, random sampling could not be employed and all eligible patients were approached for consent to participate in the study. While it may be argued that those who agreed may be different to those who declined, this did not affect this study since there was only one refusal. While the results cannot be generalized to all caregivers or all HIV infected children on treatment in South Africa, the socio-demographic characteristics of the sample renders them typical of caregivers and children living in urban based resource-limited settings.

Fifth, while there is a need for paediatric adherence longitudinal studies and this study has fulfilled this need to a certain extent, the follow-up period of this study was relatively short, namely, 6 months. Studies have shown that adherence declines over time. Thus, a longer follow-up time may have resulted in a lower cohort adherence rate.

Sixth, the exploratory nature of the study resulted in the inclusion of perhaps too many variables for the small sample size. However, this could also be seen as strength, thereby providing 'pilot data' for future studies which explore factors impacting on adherence in resource-limited settings.

Seventh, the use of virological outcome as a reference measure (gold standard) may be a contributing factor to the lack of adequate sensitivity and specificity at the various cut-offs of adherence using the various adherence measures. As noted above, several factors impact on virological suppression and for this reason it should not be considered a gold standard measurement. However, in defence of its use, amongst this treatment naïve study population, it appeared sufficiently robust as a 'gold standard' measure with those considered adherent according caregiver self-report having a 93% virological suppression rate. Though it should be borne in mind that neither adherence measures, nor virological suppression are perfect measures of adherence and therefore discrepancies between adherence classification and treatment success is expected.

Finally, several variables collected at the three time points during the 6 month follow-up, were analyzed in relation to its impact on adherence but not correlated with virological suppression due to the fact that viral load outcome was only available at one time point (month 6). The hypothesis that certain changes overtime impact on adherence was not be fully explored. The reduction in observations over time led to small samples available for meaningful results.

# CHAPTER 8
# CONCLUSIONS AND RECOMMENDATIONS

## 8.1. Introduction

To summarize, the research questions posed by the present study and elaborated on in chapter 3 were as follows: first, what is the adherence rate amongst the cohort? Second, is there agreement between the four adherence measures and viral load? Third, what is the 'best' method of adherence in a routine clinic setting? Fourth, which factors, impacting on adherence? These factors were conceptualized within four domains, namely, child, caregiver, socio-economic and health characteristics

## 8.2. Adherence Rates and utilization of Measures in a routine clinic setting

The first question pertaining to adherence rates was answered in the following manner: First, rates of adherence according to each measure were calculated. Second, the 'best' measure according to its correlation with viral load was identified through a series of regression analyses. As a result, caregiver self-reported adherence measure was identified as the best measure and used to determine the cohort adherence rate of 85%.

The researcher's experience of administering the four measures was discussed in chapter 7 in order to highlight the ease or difficulty of implementing each measure in a routine clinic setting. It was determined that pharmacy refill and clinic visit measures were the easiest to obtain and monitor and these correlated with each other as expected since both measured 'attendance'. These measures may be useful in alerting the clinician to potential adherence problems indicated by the first missed pharmacy or clinic appointment and early interventions could be instituted.

On the other hand, caregivers self-report was shown to be predictive of virological outcome. It was hypothesized that this significant agreement is conditional upon

several factors: first, it should be administered by another person and not given to the caregiver to complete and return; second, the interviewer should conduct the interview in the caregiver's first language; third, the interviewer should not be the same person responsible for the clinical care of the child.

## 8.3. Factors influencing Adherence

The evidence from this study shows that amongst all the factors in the four sub-domains socio-economic and health service characteristics have the most significant impact on adherence. Characteristics situated a priori in the child characteristics domain and impacting significantly on adherence were de facto linked to health service characteristics (such as IDC attendance prior to ARV initiation and duration of attendance).

The implications of these findings for service and further research will be discussed in the section on recommendations.

## 8.4. Recommendations

### 8.4.1. Adherence Monitoring: Implications for service delivery

Caregivers self-report, pharmacy refill and clinic visit adherence measures are useful to alert the clinician to the first signs of potential adherence problems. These methods provide a relatively easy means of monitoring adherent behaviour throughout the patient's course of treatment (life long) not only at initiation of treatment.

#### 8.4.1.1. Recommendation 1: A Multi-pronged approach to adherence monitoring

It is recommended that the health care service institute mechanisms to monitor patient adherence on an ongoing basis. This monitoring should occur on a micro level, that is, at the level of the interface between clinician and patient as well as on the macro level, that is, at the level of health service management to monitor adherence on a district of provincial level. The macro level monitoring is important because non-

adherence has public health implications regarding potential resistance and its impact on the utilization of ARV drugs. This recommendation is accompanied by a proposal for implementation, namely, the 'Algorithm for adherence monitoring in a resource-limited setting' (Figure 8.1).

The proposed approach is plausible in the South African setting for the following reasons: Firstly, in South Africa, the HIV/AIDS programme relies on 'lay counsellors' to provide counselling and support to HIV infected patients. These 'lay counsellors' often identify themselves with the same language and cultural groups of the patients and may themselves be HIV infected and on ARV treatment. This allows them to build an empathetic and trusting relationship with the patients. In this context, the health care workers could effectively administer a caregiver self-reported adherence measure based on the premise that if you want to know how the patient is doing, ask them, and then allow them to tell you without judgment! Secondly, antiretroviral drugs are scheduled drugs and have to be issued by a pharmacist, thus providing an opportunity for the involvement of the pharmacy[61]. Thirdly, the clinician or nurse has an ongoing clinical monitoring role with the patient and combining adherence monitoring will improve the realization of the goal of attaining treatment success.



***Algorithm for adherence monitoring using a multi-pronged approach***

**It is recommended** that a multi-pronged approach to monitoring adherence be used in resource-limited settings utilizing three of the measures tested in the present study, namely, caregiver self-report, pharmacy refill and clinic visits. Figure 8.1 illustrates the mechanism of this adherence monitoring system. Several members of the health care team can participate in the monitoring of adherence at various points within the health system.

[61] I am aware that pharmacists are not available full-time in every ARV clinic in which case the drugs are pre-packed and issued by either the nurse of clinician. This person therefore takes on the role of pharmacist.

***Caregiver self-report***

The cadre of workers known by several designations such as, "lay counsellors" or "patient advocates" or "expert patients", can play an important role in bridging the communication between clinicians and patients if they are language and culturally sensitive to the needs of patients. They could be instrumental in administering the caregiver self-report[62]. It is recommended that the prescribed instrument not be administered every month to avoid 'response fatigue' but that key questions are asked at every visit, for example, (1a) "have you had any difficulty giving medicines in this past month? (1b) if the answer to the previous question is "yes", and then ask, "What was the difficulty"? (1c) did this cause you to miss any doses?

The information obtained by the lay counsellor must be communicated to the clinician or nurse. Counsellors can play a role in facilitating self-efficacy skills by exploring with the caregiver how they can overcome similar problems or barriers in future.

***Pharmacy Refill***

Pharmacists have been playing an increasing role in monitoring patient adherence in the era of HAART. Increasing volumes of medication stored by patients due to repeat scripts being filled without taking into account how much is left from the previous script, could lead to patients not returning for 'on-time' collection to refill prescriptions. It is important that the pharmacist monitors on-time collections and establishes the reasons for 'late collections'. If patients report that they had sufficient medicine and didn't see the need to come on the appointed date, this could indicate that either too much medicine is being prescribed (not taking into account the amounts left at the end of each month, or patients are not being strictly adherent and thus not using the required amounts. Either way, pharmacy monitoring of refill collection dates provides an opportunity to correct either a potential problem within the health system or a problem experienced by the patient. This information should be communicated to the clinician or nurse.

[62] The PACTG caregiver self-reported adherence questionnaire was used in the present study.

***Clinic visits***

Since clinic visits are necessary for repeat prescription as well as clinical, immunological and virological monitoring, regular attendance is necessary even if the patient is feeling well. Thus monitoring on-time clinic visits is another way of identifying potential barriers to adherence. If the patient does not attend on-time, the results of the pharmacy collection and previous caregiver reports should be evaluated to identify whether there may be a problem which is also impacting on the child's adherence. It is therefore important that this monitoring be on-going and that data across the three measures are combined into one reporting system (namely, the patient folder) to provide easy access to all concerned with the patient's care.

At the level of health management, it is suggested that the rates of 'on-time' clinic visits be used as an indicator of adherence (at clinic, district and provincial level) by health managers. This data provides information for health service planning which includes the identification of staffing and resource needs in an ongoing manner. At present data on the number of patients on ARVs per month, including information on patient attrition is collected in the Western Cape Province, for example. The proposed system of monitoring will add another dimension to the existing data collection by establishing patterns of clinic attendance by those remaining on treatment. The current system of defaulter tracking relies on clinic visit records. However, the lost opportunity for timeous intervention caused by the broad definition of 'defaulter'[63] renders this system ineffective to deal with potential adherence problems and renders this system merely as a 'policing' tool to find errant patients.

Thus, the multi-pronged approach outlined above, if implemented synergistically within the system will help to identify potential adherence problems before treatment failure or 'defaulting'.

It is further recommended that this proposed system of adherence monitoring be implemented and evaluated to test this hypothesis. The system requires piloting to determine acceptability amongst health care workers and the development of the structure of the counselling interventions. Subsequent to the pilot study, a randomized

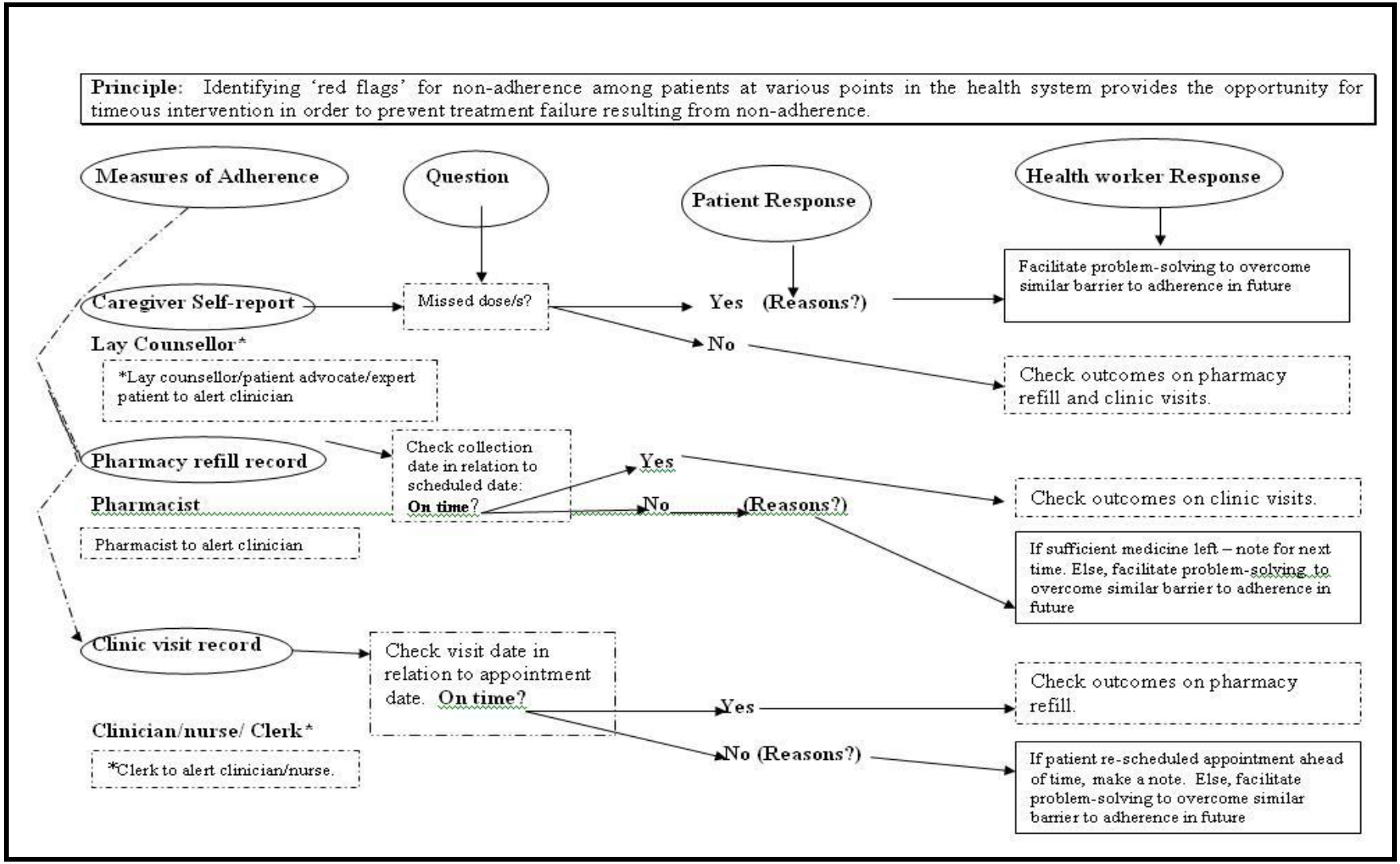
[63] There is currently no standard definition of a 'defaulter' in South Africa. Definitions range from patients who missed the clinic visit for more than one week to 'someone who has missed the clinic appointment by more than 2-3 months and cannot be traced."

controlled trial should be conducted to evaluate the impact of the intervention on adherence.

***What is the role of viral load measurement in adherence monitoring?***

The above-mentioned proposal does not exclude virological monitoring which has a place in monitoring treatment success and alerting the clinician to treatment failure which may result from resistance. However, it should be used as an adjunct to adherence monitoring and not in place of adherence monitoring.

**Figure 8.1: Algorithm for Adherence monitoring in resource-limited setting**



### 8.4.2. Adherence enhancing interventions

A review of the literature outlined in chapter 2 indicated that the few empirically test adherence enhancing interventions were generally very intensive and required at times a huge investment in resources, especially human resources, without the corresponding magnitude of success expected from such investment. It is against this background that the following recommendations are made based on the evidence from the present study as well as other relevant studies.

#### 8.4.2.1. Recommendation 2: Paediatric-specific treatment literacy training

**It is recommended** that an evidenced based generic paediatric treatment literacy guide and concomitant training initiatives be developed aimed at educating caregivers and health care workers on paediatric specific HIV treatment in South Africa. At present, there is no co-ordinated strategy to address the lack of education and awareness around paediatric ARV treatment in South Africa.

The main finding in this study, regarding the impact of counselling by a counsellor prior to ARV initiation on adherence, highlights the importance of clear communication between caregivers and health care providers regarding the implications and scope of ARV treatment in children. There is a paucity of data to support a standardized approach to paediatric treatment literacy. However, the increasing number of HIV infected children in Sub-Saharan Africa demands a change in the status quo. It is important that clear and consistent messages relating to paediatric HIV management and treatment be articulated. No one can dispute the value of providing information and ensuring that the patient has sufficient knowledge about his/her (or the child's) condition and therapy.

#### 8.4.2.2. Recommendation 3: A Family-centred Model of Care

Evidence from this study showed that children who had other members of the household infected with HIV were less likely to be adherent.

**It is recommended** that a 'one-stop' clinic visit which ensures that at the minimum, the caregiver is included in the clinical consultation with the child as an important proactive intervention which can impact positively on adherence. The ideal situation is to have all members of the family encouraged to seek HIV testing and health care monitoring, especially siblings of the index child.

Health care delivery at the primary care level using the 'general practitioner' approach where all members of the family could receive health care at the same visit, would facilitate such a family-centred model of care. This should include uninfected caregivers and siblings of children on treatment. For example, grandmothers who are primary caregivers may not be HIV-infected but may suffer with chronic diseases such as hypertension, diabetes and rheumatism which will impact on their quality of life and care-giving roles. The health system should be able to support the clinician's ability to enquire after the health of the caregiver and do something about any problem identified, including depressive symptoms in the caregiver.

#### 8.4.2.3. Recommendation 4: Training Health care workers

**It is recommended** that the transfer of knowledge and skills to health care workers, especially nurses at the primary level be scaled up[64] in South Africa in order to increase the capacity of the health system to render family-centred care at primary care level which includes paediatric HIV management and treatment

As discussed in chapter 2, there is a 'fear' amongst many clinicians and nurses in South Africa regarding paediatric HIV management and treatment. Demystifying paediatric HIV management and treatment will be the first step in the process of setting up a family-centred model of care at primary care level. These recommendations are made despite the knowledge that South Africa and many Sub-Sahara African countries are facing a health care worker crisis but the current vertical and specialist approach to paediatric management and treatment is not sustainable. It

[64] The Provincial Government of the Western Cape's Health Department has implemented the policy of 'mentorship training of primary care clinicians by paediatricians at tertiary level care, since 2006.

is acknowledged that a certain amount of specialist expertise (and therefore specialist patient care) is necessary within the ever-changing field of HIV and AIDS.

#### 8.4.2.4. Recommendation 5: Early identification of HIV- infected children

Children in this study cohort were relatively young, some as young as 3 months old. The data further showed that attendance at the IDC outpatient clinic prior to initiation of ARV treatment impacted positively on adherence. It is therefore imperative to identify HIV-infected children very early in order to bring them into care and commence the practice of administering life saving drugs, initially with PJP prophylaxis, treatment of opportunistic infections and later with antiretrovirals[65].

#### 8.4.2.5. Early identification of HIV- infected children

**It is recommended** that the early identification of HIV infected children is entrenched in every contact between the health service and patients. [66]

Clearly a successful PMTCT programme will go a long way to facilitating this by identifying and tracking HIV-exposed children. Should PMTCT programmes fail to follow-up HIV exposed children, these children should not be allowed to be 'lost in the system' and opportunities during immunization visits should be utilized to do routine HIV screening of infants. A further opportunity for identifying HIV-infected children is to 'trace' any off-spring of adults testing HIV positive at voluntary counselling testing services[67]. In this way, initiating ARV treatment may not have to be dealt with as an 'emergency' as it often is in this setting due to children being identified when they are severely immune-compromised.

---

[65] Currently HIV-exposed infants in South Africa are offered co-trimoxazole for Pneumocystis Carinii pneumonia (PCP) prophylaxis started at four to six weeks of age, free formula for six months if requested by the mother and diagnostic Polymerase CHAIN reaction (PCR) HIV testing beginning at six weeks of age. ARV therapy is offered to HIV-infected children with prolonged or recurrent hospitalization, those children classified with WHO clinical stage 3 or 4 disease, or those with CD4 cell percentages below 20 percent if younger than 18 months of age.(see www.doh.gov.za/docs/index.html )

[66] This recommendation is given with the proviso that caregiver education is provided and public awareness is created regarding paediatric HIV management and treatment (especially in the light of the implications of the CHER study recommendations, as commented on in Chapter 2 section 2.12.1).

[67] Adults testing HIV positive should be asked whether they have any children (even if they are male!). If they do, they should be encouraged to bring their children for HIV testing as well.

## 8.5. Recommendations for future research

Firstly, the support for the proposal to introduce an explicit discipline within biopharmaceutics called pharmionics,[68] is reiterated here. This recommendation is made on the premise that this will encourage financial support for quality research regarding adherence in the broadest sense but especially with regard to paediatric antiretroviral treatment adherence especially in resource-poor settings.

It is therefore imperative that first, studies are carried out using larger sample sizes[69] to further investigate measurement and correlates of adherence among children in resource-limited settings. If the relatively high rates of adherence as demonstrated in the present study and other studies emerging from resource-limited settings are true, then large sample sizes are required to detect an effect. Factors which emerged as statistically significant or marginally significant in this study should be further explored. There is a need for further quantitative data to determine the impact of various barriers to non-adherence, especially within the health system and within the socio –economic domain. Large-scale government and health service interventions can have a direct impact by removing barriers which may be out of the control of individual patients to effect change in these domains.

Second, defined age cohorts should be studied since results cannot be generalized across various age groups, a problem which was identified through the literature review and discussed in chapter 2.

Third, study designs should be longitudinal with a minimum of 6 months follow-up. It has been found that levels of adherence decline over time. For this reason, barriers identified during the first few months of treatment may be different to barriers which impact on long-term adherence. We have sufficient data to prove that cross-sectional adherence studies are no longer viable for exploring the complexities of adherence related behaviours and influences.



[68] The proposal by Vrijens (2005) was described in Chapter 2 (2.13).
[69] multi-site studies is one manner in which the problem of inadequate sample sizes may be overcome

Fourth, choices of adherence measures and 'gold standard' measures used in paediatric adherence studies should be carefully considered in the context of resource limited settings. Further research into the validation and development of 'user-friendly' adherence measurement tools such as those tested in the present study, with adaptations to increase specificity.

Finally, research into the development and evaluation of adherence interventions in the context of resource-limited settings are required to maintain these present relatively high levels of adherence to HAART reported in these settings. These include research into health systems factors which may impact on adherence as discussed.

# REFERENCES


3Cs4kids Analysis and Writing Committee. 2008. *Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis*. *AIDS.* 22(1): 97-105.

Adam, B., Maticka-Tyndale, E. & Cohen, J. 2003. Adherence practices among people living with HIV. *AIDS Care.* 5(2): 263-274.

Ahoua, L. et al. 2007. Children's antiretroviral treatment outcomes after 12 and 24 months of HAART in an HIV care program in North-western Uganda. [Abstract]. *Fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. 23-25 July 2007,* Sydney, Australia.

Al-Omran, O., MacAdam, A. & Gard, P. 2000. Factors affecting medication adherence in Saudi Children. *The Pharmaceutical Journal.* 265: 7114.

Arrivé, E. et al. 2005. Assessment of adherence to highly active antiretroviral therapy in a cohort of African HIV-infected children in Abidjan, Cote d'Ivoire. *Journal of Acquired Immune Deficiency Syndrome.* 40(4): 498-500.

Austin, P. 2003. African women and HIV/AIDS: a social work perspective. Masters Thesis. Department of Social Work, University of Pretoria.

Bachanas, P. et al. 2001. Predictors of psychological adjustment in school-aged children infected with HIV. *Journal of Paediatric Psychology.* 26: 343-352.

Banez, G.A. & Compas, B. 1990. Children's and parents' daily stressful events and psychological symptoms. *Journal of Abnormal Child Psychology.* 18: 591-605.

Bangsberg, D. R., Hecht, F. & Charlebois, E. D. 2000. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS* 14: 597-607.

Barron, P. et al. 2006. *District health barometer 2005/06*. Durban: Health Systems Trust.

Belzer, M. E. et al. 1999. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *Journal Adolescent Health*. 25: 316-319.

Benjamin, D.K. et al. 2004. Growth patterns reflect response to antiretroviral therapy in HIV-positive infants: potential utility in resource-poor settings. *AIDS Patient Care and STDS* . 18(1): 35-43.

Bennetts, A. et al.1999. Determinants of depression and HIV-related worry among HIV-positive women who have recently given birth, Bangkok, Thailand. *Social Science & Medicine* 49 (6): 737-749.

Berrien, V.M. et al. 2004. Adherence to antiretroviral therapy in HIV-infected paediatric patients improves with home-based intensive nursing intervention. *AIDS Patient Care and STDS*. 18: 355-363.

Bikaako-Kajura, W. et al. 2006. Disclosure of HIV status and adherence to daily drug regimens among HIV-infected children in Uganda. *AIDS Behavior.* 10: S85-S93.

Bock, P. 2006. Monthly ARV Statistics for Western Cape Province. Provincial Government Health Department of the Western Cape. [Personal communication, 25 January]. Cape Town. (Unpublished).

Boland, R., Moore, J. & Schuman, P. 1999. The longitudinal course of depression in HIV-infected women. [Abstract]. *Psychosomatics*. 40: 160.

Boni, S. et al. 2000. Factors influencing physicians' judgments of adherence and treatment decisions for patients with HIV disease. *Medical Decision Making.* 21: 28-36.

Boyle, B. 2000. Antiretroviral therapy in children, women and intravenous drug users.[Online]. Available: http://www.hivandhepatitis.com/recent/women/102500.html . [2004, February 12].

Brackis-Cott, E. et al. 2003. Paediatric HIV medication adherence: the views of medical providers from two primary care programs. *Journal of Paediatric Health Care.* 17(5): 252-260.

Bradshaw, D. et al. 2005. Provincial mortality in South Africa, 2000 - priority-setting for now and a benchmark for the future. *South African Medical Journal*. 95(7): 496-503.

Brandt, R. 2007. Does HIV matter when you are poor and how? The impact of HIV/AIDS on the psychological adjustment of South African mothers in the era of HAART. Doctoral Thesis. Department of Psychology, University of Cape Town.

Brouwer, C. et al. 2000. Psychosocial and economic aspects of HIV/AIDS and counselling of caretakers of HIV-infected children in Uganda. *AIDS Care*. 12: 535-540.

Brown, L., Lourie, K. & Pao, M. 2000. Children and adolescents living with HIV and AIDS: a review. *Journal of Child Psychololgy and Psychiatry*. 41(1): 81-96.

Byrne, M. et al. 2002. Achieving adherence with antiretroviral medications for paediatric HIV disease. *AIDS Reader*. 12: 151-164.

Catalan, J. & Burgess, A. 1996. HIV-associated dementia and related disorders. *International Review of Psychiatry*. 8: 237.

Catz, SL. et al. 2000. Patterns, correlates and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychology*. 19(2): 124-133.

Cederfjäll, C. et al. 2002. Self-reported adherence to antiretroviral treatment and degree of sense of coherence in a group of HIV-infected patients. *AIDS Patient Care and STDs*. 16(12): 609-616.

Chesney, MA. 2000a. Factors affecting adherence to antiretroviral therapy. *Clinical Infectious Diseases*. 30(2): 171-176.

Chesney, MA. et al. 2000b. Patient Care Committee and Adherence Working Group of the outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). Self-reported adherence to antiretroviral medication among participants in HIV Clinical Trials: the AACTG Adherence instrument. *AIDS Care*. 12(3): 255-266.

Chesney, M. 2003. Adherence to HAART regimens. *AIDS Patient Care and STDs*.17(4): 169-177.

Cheung R. et al. 1998. Compliance with anti-tuberculous therapy: A field trial of a tablet-box with a concealed electronic recording device. European Journal of Clinical Pharmacology. 35: 401-407.

Children's Rights Centre. 2005. Preliminary National Consultation on Paediatric HIV/AIDS Treatment Advocacy: a meeting called by the Children's Rights Centre and Médecins sans Frontières, 31st January. Durban, South Africa. (Unpublished).

Cluver, L., Gardner, F. & Operario, D. 2007. Does orphanhood by AIDS matter? A controlled study of psychological distress amongst AIDS-orphaned children in urban South Africa. *Journal of Child Psychology and Psychiatry*. 48(8): 755-763.

Coetzee, D. et al. 2004. Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. *AIDS*. 18(3): S27-S31.

Coetzee, D. 2005. Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa. *Bulletin of the World Health Organisation.* 83(7): 489- 494.

Cohen, J. et al. 2003. *Applied multiple regression/correlation analysis for the behavioral sciences*. 3rd ed. New Jersey, USA: Lawrence Erlbaum Associates.

Corbett, A. et al.2005. Pharmacokinetics between trade and generic liquid and split tablet formulations of Lamivudine, Stavudine and Nevirapine in HIV-infected Malawian children. [Abstract] *45th Interscience Conference on Antimicrobial Agents and Chemotherapy.16-19 December,* Washington DC.

Cramer, JA. et al. 1989. How often is medication taken as prescribed? A novel assessment technique. *JAMA*. 261: 3273-3277.

Crystal, S. et al. 2001. Initiation and continuation of newer antiretroviral treatment among Medicaid recipients with AIDS. J Gen Intern Med. 16(12): 850-859.

Cunningham, PB. et al. 2006. Achieving adherence to antiretroviral medications for paediatric HIV disease using an empirically supported treatment: a case report. J Dev.Behav Pediatr. 27(1): 44-50.

Davies, M.-A.et al.2007. Adherence to antiretroviral medication in children measured by medication returned and questionnaires. 3rd South African AIDS Conference, 5-8 June, Durban, South Africa.

De Civita, M. & Dobkin, P. 2004. Paediatric adherence as a multidimensional and dynamic construct, involving a triadic partnership. Journal of Paediatrics Psychology. 29(3): 157-169.

De Groot R. 2000. Treating HIV-positive children: the Dutch perspective: Optimising Paediatric HIV Care. [Online]. Available: http://www.i-base.org.uk/pub/paed/dutch.html. [2003, November 3].

DeMatteo, D. et al. 2002. The 'family' context of HIV: a need for comprehensive health and social policies. *AIDS Care*. 14(2)261-278.

Department of Health. 2000. *HIV/AIDS STD strategic plan for South Africa: 2000-2005.* [Online]. Available: http://www.doh.gov.za/aids/docs/aids-plan/ [2008, February 16].

Department of Health. 2001. *Policy guidelines for youth and adolescent health* . [Online]. Available: http://www.doh.gov.za/docs/policy/yah/index.html . [2008, February 16].

Department of Health. 2003. *Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa.* [Online]. Available: http://www.gov.za/docs. [2003, November 19].

Department of Health. 2005. Concerned paediatricians of South Africa: a meeting called by the National Department of Health on 15 November 2005, Johannesburg. (Unpublished).

Department of Health. 2006. *Correction: More than 235000 benefiting from ARV Programme.* [Online]. Available: http://www.doh.gov.za/docs/pr/pr1117-f.html . [2006, December 11].

Department of Health. 2007a. *HIV & AIDS and STI Strategic Plan for South Africa 2007-2011*. Pretoria: Government Printers.

Department of Health. 2007b. *National HIV and Syphilis Antenatal sero-prevalence survey in South Africa 2006.* Pretoria: Government Printers.

Department of Health. 2008. Policy and guidelines for the implementation of the PMTCT programme. [Online] Available: http://www.doh.gov.za/index.html. [2008, February 5]

Deschamps, D., Flandre, P. & Calvez, V. 2000. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Journal of the American Medical Association. 283(2): 205-211.

Dolezal, C. et al. 2003. The reliability of reports of medical adherence from children with HIV and their adult caregivers. *Journal of Paediatric Psychology*. 28 (5): 355-361.

Dolan, S. 2006. Saving lives: children's right to HIV and AIDS treatment. [Online]. Available: http://www.unicef.org/aids/index_34187.html [2008, February 16].

Dorrington, R. et al. 2006. The Demographic Impact of HIV/AIDS in South Africa: National and Provincial Indicators for 2006. The UCT Centre for Actuarial Research, South African Medical Research Council Burden of Disease Unit and Actuarial Society of South Africa. [Online] Available: http://www.hivan.org.za/admin/documents/ASSA2003Indicators.pdf. [2006, December, 6].

Doyle, P. & Millar, D. 1990. A General Description of an Actuarial Model Applicable to the HIV Epidemic in South Africa. *Transactions of the Actuarial Society of South Africa*. 561-593.

Dreyfuss, M.L. et al. 2001. Determinants of low birth weight among HIV-infected pregnant women in Tanzania. *American Journal of Clinical Nutrition.* 74(6): 814-826.

Durante, A. et al. 2003. Home-based study of anti-HIV drug regimen adherence among HIV- infected women: feasibility and preliminary results. *AIDS Care*. (15): 103-115.

Durvasula, R. et al. 2002. Differential predictors of HAART adherence as a function of gender. [Abstract] XIV International AIDS Conference, July 7 - 12 Barcelona, Spain.

Dutschke, M. 2007. *Defining children's constitutional right to social services: children's Institute*. Cape Town: University of Cape Town.

Eldred, L. 1997. *Adherence in the era of protease inhibitors: Hopkins HIV report.* Washington, D.C.: John Hopkins University, AIDS Service.

Eley, B et al. 2004. Initial experience of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents. *South African Medical Journal.* 94 (8): 643-646.

Eley, B et al. 2006a. Antiretroviral treatment for children. *South African Medical Journal.* [Online] 96 (9): 988-993.

Eley, B. 2006b. Addressing the paediatric HIV epidemic: a perspective from the Western Cape Region of South Africa. *Transactions of the Royal Society of Tropical Medicine & Hygiene.* 100 (1): 19-23.

Ellis, DA et.al 2004. Use of multisystemic therapy to improve regimen adherence among adolescents with type 1 diabetes in poor metabolic control: a Pilot study. *Journal of Clinical Psychology in Medical Settings*. 11: 315-324.

Essajee, S. et al. 1999. Immunologic and virologic responses to HAART in severely immunocompromised HIV-1-infected children. *AIDS*. 13: 2523-2532.

Farley J. 2001. Adherence to HIV Therapy in Preadolescent Children: Where do we go from here? [Online] http://www.hivfiles.org/adherence.pdf. [2004, February 12].

Farley, J. et al. 2003. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. *Journal of Acquired Immune Deficiency Syndrome*. 33(2): 211-218.

Fassinou, P. et al. 2004. Highly Active antiretroviral therapies among HIV-1-infected children in Abidjan, Côte d'Ivoire. *AIDS.* 18: 1905-1913.

Fennie, K.P., Bova, C.A., & Williams, A.B. 2006. Adjusting and Censoring Electronic Monitoring Device Data: Implications for Study Outcomes. *Journal of Acquired Immune Deficiency Syndrome*. 43(Supplement 1): S88-S95.

Flanders, PA. & McNamara, J. 1984. Prediction of compliance with an over-the-counter acne medication. *Journal of Psychology*. 118: 31-36.

Fletcher, W., Pappius, E.M., & Harper, S. 1979. "Measurement of medication compliance in a clinical setting. *Archives of Internal Medicine*. 139: 635-638.

Fletcher, C.V. 2004. Antiretroviral therapy for HIV-infected infants: progress and pitfalls. *AIDS*. 18: 325-326.

Flexner, C. 1998. HIV-protease inhibitors. *New England Journal of Medicine*. 338(18): 1281-1292.

Fogarty, L. et al. 2002. Patient adherence to HIV medication regimens: a review of published literature and abstract reports. *Patient Education and Counselling*. 46(2): 93-108.

Forsyth, B et al. 2005. Secrecy in South Africa: Factors affecting a pregnant woman's ability to disclose her HIV+ status to others. 7th International AIDS Impact Conference. 4-7 April, 2005, Cape Town, South Africa.

Fotheringham, M.H. & Sawyer, M.G. 1995. Adherence to recommended medical regimens in childhood and adolescence. *Journal of Paediatric Child Health*. 31: 72-78.

Frick, P.A et al. 1998.Antiretroviral medication compliance in patients with AIDS. *AIDS Patient Care and STDs.* 12: 463-469.

Gao, X. & Nau, D.P. 2000. Congruence of three self-report measures of medication adherence among HIV patients. *Annals of Pharmacotherapy*. 34: 1117-1122.

Garvie, P. A. et al. 2003. Adherence to Therapy Regimens by Paediatric Patients with HIV Infection. *Behavioral Medicine*. [Online]. Available: http://www.stjude.org/content/files/1/7300_06_Behavioral_Medicine.pdf. 2003. [2004 February 12].

Garvie, P.A., Lensing, S. & Rai, S.N. 2007. Efficacy of a Pill-Swallowing Training Intervention to Improve Antiretroviral Medication Adherence in Pediatric Patients with HIV/AIDS. *Pediatrics.* 119(4): e893-e899.

Giacomet, V. et al. 2003.Adherence to antiretroviral therapy and its determinants in children with human immunodeficiency virus infection: a multicentre, national study. *Acta Paediatrica.* 92(12): 1398-1402.

Gibb, D. M et al. 2003. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Paediatric Infectious Diseases Journal*. 22(1): 56-62

.

Gigliotti, F., Murante, BL. & Weinberg, GA. 2001. Short course Directly Observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Paediatric Infectious Diseases Journal*. 20: 716-718.

Gilbert, J.R. et al. 1980. Predicting compliance with a regimen of digoxin therapy in family practice. *Canadian Medical Association Journal*.123: 119-122.

Global Movement for Children, (GMC). 2006. Saving Lives - Children's Right to HIV and AIDS Treatment. [Online] Available: http://www.reliefweb.int/rw/lib.nsf/db900SID/AMMF-6W3KJH?OpenDocument [2007, July 25]

Goetz, M.B & Rossman, B.L. 1998. Evaluation of predictors of adherence in HIV-infected patients receiving combination anti-retroviral therapy. [Abstract] *12th World AIDS Conference on AIDS. 12 June 1998,* Geneva.

Goode, M.A. et al. 2003. Adherence issues in children and adolescents receiving highly active antiretroviral therapy. *AIDS Care*. 15(3): 403-408.

Gordillo, V. et al.1999. Sociodemographic and psychological variables influencing adherence to antiretroviral therapy. *AIDS.* 13: 1763-1769.

Grandin, W. et al. 2006. Deaths at Red Cross Children's Hospital, Cape Town 1999-2003: a study of death notification forms. *South African Medical Journal*. 96(9 Part 2): 964-968.

Griffin, G.E. 1990 Malabsorption, malnutrition and HIV disease. *Baillieres Clinical Gastroenterology*. 4(2): 361-373.

Gross, R. et al. 2001. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS*. 15: 2109-2117.

Grossberg, R., Zhang Y. & Gross, R. 2004. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. *Journal of Clinical Epidemiology*. 57(10): 1107-1110.

Hammami, N. et al. 2004. Integrating adherence to highly active antiretroviral therapy into children's daily lives: a qualitative study, *Paediatrics.* 114(5): e591-e597.

Hann, D., Winter, K., & Jacobsen, P. 1989. Measurement of depressive symptoms in cancer patients: Evaluation of the Centre for Epidemiological Studies Depression Scale (CES-D). *Journal of Psychosomatic Research*. 46: 437-443.

Hansudewechakul, R. et al. 2006. A comprehensive programme to strengthen adherence to antiretroviral drug therapy and achieve virological control in HIV infected children in Thailand. *Vulnerable Children and Youth Studies*. 1 (2): 180-191.

Haubrich, R.H. et al. 1999. The value of patient reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS* 13(9):1099-1107.

Havlir, D.V. et al. 2000. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *Journal of the American Medical Association*. 283 (2): 229-234.

Heath, K. et al. 2002/ Intentional Non-adherence due to Adverse Symptoms Associated with Antiretroviral Therapy. *Journal of Acquired Immune Deficiency Syndrome*. 31: 211-217.

HIV/AIDS Directorate. 2004. Western Cape Antiretroviral Treatment Programme Monthly Report, Provincial Government of the Western Cape. (Unpublished).

HIV/AIDS Project Development and Evaluation Unit (HAPDEU).2001.Treatment Adherence: Report. [Online] Available: http://depts.washington.edu/hapdeu/web/adherence/Report/TAP_Guide.htm. [2003, December 11].

Hogg, R.S. et al. 2000. Nonadherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women. [Abstract # 73]. 7th Conference on Retroviral Opportunistic Infections. Jan 30- Feb 2 2000, Vancouver, Canada. [2004, November, 12]

Hogg, R.S. et al. 2002. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* 16: 1051-1058.

Holzemer, W.L. et.al 1999. Predictors of self-reported adherence in persons living with HIV disease. *AIDS Patient Care and STDs.* 13: 185-197.

Horberg, M. et al. 2008. Effects of depression and selective serotonin reuptake inhibitor use on adherence to highly active antiretroviral therapy and on clinical outcomes in HIV-infected patients. [In print]. *Journal of Acquired Immune Deficiency Syndrome*. January 31.

Huba, G. et al. 1997. Adherence to Protease Inhibitor Combination Therapy among Youth: A Report from a Focus Group on issues for Youth Living with HIV. [Online]. Available: http://www.themeasurementgroup.com/hivaids/spns/edc.htm.[2004, January 6]

Human Sciences Research Council 2004, Nelson Mandela Study on HIV/AIDS in Children: Full Report. [Online] Available: http//www.hsrcpress.ac.za. [2005, July 24].

Hurwitz, J et al. 1998. Adherence to HIV Therapies: Utilizing Adherence Modules in PACTG Protocols. [Abstract] *IMPAACT Meeting*. December 1998. Washington, DC.

Hutton, N. & Oleske, J. M. 2005. The Care of Children & Adolescents: In *A Clinical Guide to Supportive & Palliative Care for HIV/AIDS.* [Online]. Available: http://hab.hrsa.gov/tools/palliative/chap12.html [2006, February 15].

Ickovics, J.R. & Meisler, A.W. 1997.Adherence in AIDS clinical trials: a framework for clinical research and clinical care. *Journal of Clinical Epidemiology.* 50(4): 385-391.

IMPAACT Adherence to Therapy Subcommittee. Adherence Modules.2000. [Online] Available: https://www.fstrf.org/apps/cfmx/apps/actg/html/QOLFormsIMPAACT/pedadhere.html [2004, September 9]

International Treatment Preparedness Coalition.2006. Missing the Target: A report on HIV/AIDS Treatment Access from the Frontlines. [Online] Available: http://alp.org.za.dedi20a.your-server.co.za/images/upload/ITPC28Nov06.pdf. [2007, June 6].

Jacobson, A. et al.1990. Adherence among children and adolescents with insulin-dependent diabetes mellitus over a four-year longitudinal follow-up:1: The influence of patient coping and adjustment. *Journal of Paediatric Psychology.* 15(4): 511-526.

Joint Civil Society Monitoring Forum and Department of Health. Antiretroviral Treatment Roll-out Progress Report 2003-2006. Source : Dr Kalumba's Office, National Department of Health .[Email communication 2007, May 30]. (Unpublished).

Joint UN Programme on HIV/AIDS. 2007. *AIDS Epidemic Update.* [Online]. Available: http://www.unaids.org/en/pub/HIVData/EpiUpdate/EpiUpdArchive/2007/. [2008, January 15].

Kaharuza, F.M et al. 2006. Depression and CD4 cell count among persons with HIV infection in Uganda: *AIDS*. 10: S105-S111.

Katko, E. et al. 2001. Assessment of Adherence with Medications in Human Immunodeficiency virus-infected children. *Journal of Paediatric Infectious Diseases*. 20(12): 1174-1176.

Keogh, P. et al. 1994. The social impact of HIV infection on women in Kigali, Rwanda: a prospective study. *Social Science and Medicine.* 38: 1047-1053.

Kimmerling, M., Wagner, G. & Ghosh-Dastidar, B. 2003. Factors associated with accurate self-reported adherence to HIV antiretrovirals. *International Journal of STD & AIDS*.14: 281-284.

King, J.R. et al. 2002. Antiretroviral Pharmacokinetics in the Paediatric Population: A Review. *Clinical Pharmacokinetics.* 41: 1115-1133.

Kline, M. 2004. Paediatric HIV Infection. [Online] Available: http://bayloraids.org/resources/pedaids/manifestations.shtml. [2004, April 21]

Knobel, H. et al. 2002. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. *AIDS.* 16: 605-613.

Kruse, W. et al. 1992. Measurement of drug compliance by continuous electronic monitoring: A pilot study in elderly patients discharged from hospital. *Journal of the American Geriatrics Society*. 40: 1151-1155.

Lallemant, M. et al. 2004. Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand. *New England Journal of Medicine.* 351(3): 217-228.

Ledlie, S.W. 2001. The psychosocial issues of children with perinatally acquired HIV disease becoming adolescents: a growing challenge for providers. *AIDS Patient Care and STDs.*15(5): 231-236.

Lesch, A. et al. 2007. Paediatric HIV/AIDS disclosure: towards a developmental and process-oriented approach. *AIDS Care*. 19(6): 811-816.

Lewinsohn, P.M. et al. 1997. Centre for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychological Aging* 12: 277-287.

Liu, H. et al. 2001.A comparison Study of Multiple Measures of Adherence to HIV Protease Inhibitors. *Annals of Internal Medicine*. 134(10): 968-977.

Mannheimer, S. B. et al. 2006. The CASE adherence index: A novel method for measuring adherence to antiretroviral therapy. *AIDS Care*. 18(7): 853-861.

Marhefka, S.L. et al. 2004. Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP). *AIDS Care*. 16(3): 323-337.

Marhefka, S. L. et al. 2006. Brief report: assessing adherence to paediatric antiretroviral regimens using the 24-hour recall interview. *Journal of Paediatric Psychology*. 31(9): 989-994.

Markowitz, M. 2007. Resistance, fitness, adherence, and potency: mapping the paths to virologic failure. *Journal of the American Medical Association*. 282(2): 250-251.

Martin, S. et al. 2007. Patient, caregiver and regimen characteristics associated with adherence to highly active antiretroviral therapy among HIV infected children and adolescents. *Journal of Paediatric Infectious Diseases*. 26: 61-67.

Martinez, J. et al. 2000. Adherence to antiviral drug regimens in HIV-infected adolescent patients engaged in care in a comprehensive adolescent and young adult clinic. *Journal of the National Medical Association*. 92: 55-61.

Mathews, G. et al. 2002. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. *AIDS.* 16(1):53-61.

Mazzuca, S. 1982. Does patient education in chronic disease have therapeutic value? *Journal of Chronic Diseases.* 7: 521-529.

McComsey, G. et al.2003. Impact of protease inhibitor substitution with Efavirenz in HIV-Infected Children: Results of the first paediatric switch study. *Pediatrics*.111(3): e275-e281.

McNabb, JJ. et al. 2003. Patterns of adherence to antiretroviral medications: the value of electronic monitoring. *AIDS*. 17:1763-1767.

Measurement Excellence and Training Resource Information Center. 2002. Critical review of Center for Epidemiologic Studies Depression Scale (CES-D). [Online] Available: http://www.measurementexperts.org/instrument/instrument_reviews. [2006, June 5].

Médecins sans Frontières. 2006. Too little for too few: Challenges for effective and accessible antiretroviral therapy.[Online] Available: http://www.msf.ca/aids2006/files/REP_IACbriefingdoc_en.pdf .[2006, August 15].

Mellins, C. A. et al. 2000. Psychosocial factors associated with adaptation in HIV-infected mothers. *AIDS and Behavior*. 4: 317-328.

Mellins, C. A. et al. 2004. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Journal of Paediatric Infectious Diseases*. 23(11): 1035-1041.

Michaels, D. et al. 2006a. *Exploring current practices in paediatric ARV rollout and integration with early childhood programs in South Africa: A rapid situational analysis. Population Council Inc. Horizons Final Report*. Washington, DC: Population Council.

Michaels, D. et al. 2006b. *Expanding paediatric access to antiretroviral therapy in South Africa. Horizons Research Summary*. Washington, DC: Population Council.

Michaels, D. & Eley, B. 2007. The HIV/AIDS and STI National Strategic Plan 2007-2011: a paediatric perspective. South African Journal of Health. 1(4): 135-139.

Michaels, D. & Nuttall, J. 2006. Antiretroviral Treatment Literacy for Caregivers of Children on Treatment: A Counsellor's Guide. (Unpublished).

Milan, S. et al. 2005. Interpersonal predictors of depression trajectories in women with HIV. *Journal of Consulting and Clinical Psychology.* 73: 678-688.

Miles, M.S., Gillespie, J.V. & Holditch-Davis, D. 2001. Physical and mental health in African American mothers with HIV. *Journal of the Association of Nurses in AIDS Care.* 12: 42-50.

Mills, E.J. 2006. Adherence to antiretroviral therapy in Sub-Saharan Africa and North *America. Journal of American Medical Association*. 296: 679-690.

Mills, E.J. et al. 2006. Adherence to HAART: a systematic review of developed and developing nation patient reported barriers and facilitators. *PLoS Medicine*. 3(11): e438.

Mocroft, A. et al. 2003. Virological rebound after suppression on highly active antiretroviral therapy. *AIDS.* 17(12): 1741-1751.

Mofenson, L.M. et al. 1997. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *Journal of Infectious Diseases.* 175: 1029-1038.

Morisky, D.E., Green, L.W. & Levine, D.M. 1986.Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care*. 24: 67-74.

Moulding, T., Onstad, G.D. & Sbarbaro, J.A. 1970. Supervision of outpatient drug therapy with the medication monitor. *Annals of Internal Medicine.* 73: 559-564.

Mukhtar-Yola, M. et al. 2006. Preliminary investigation of adherence to antiretroviral therapy among children in Aminu Kano Teaching Hospital, Nigeria. *African Journal of AIDS Research.* 5(2): 141-144.

Müller, A. et al. 2008. Electronic measurement of adherence to paediatric antiretroviral therapy in South Africa. *The Paediatric Infectious Disease Journal.* 27(3):1-6.

Murphy, D.A. et al. 2001. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort. *AIDS Care*. 13: 27-40.

Murphy, DA. et al. 2003. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Archives of Paediatrics Adolescent Medicine*.157 (3): 249-255.

Murri, R. et al. 2002. Physician Estimates of Adherence and the Patient-Physician Relationship as a Setting to Improve Adherence to Antiretroviral Therapy. *Journal of Acquired Immune Deficiency Syndrome*.31: S158-S162.

Myers, J.K. & Weissman, M.M. 1980. Use of a self-report symptom scale to detect depression in a community sample. *American Journal of Psychiatry.* 137:1081-1084.

Myung, P. et al. 2007. Directly Observed Highly Active Antiretroviral Therapy for HIV-Infected Children in Cambodia. *American Journal of Public Health.* 97(6): 974-977.

Naar-King, S. et al. 2005. Measuring adherence to treatment of paediatric HIV/AIDS. *AIDS Care.* 17(3): 345-349.

Naar-King, S. et al. 2006. Healthy choices: motivational enhancement therapy for health risk behaviors in HIV-positive youth. *AIDS Education and Prevention*. 18(1): 1-11.

Nabukeera-Barungi, N. et al. 2007. Adherence to antiretroviral therapy in children attending Mulago Hospital, Kampala. *Annals of Tropical .Paediatrics*. 27(2): 123-131.

Nachega, J.B. et al. 2004. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. *AIDS Research and Human Retroviruses*. 20(10): 1053-1056.

Nannan, N. et al. 1998. What is the infant mortality rate in South Africa? The need for improved data. *South African Medical Journal*. 88(12) 1583-1587.

Nattrass, N. 2006. Disability and welfare in South Africa's era of unemployment and AIDS. Centre for Social Science Research Working Paper No.147. University of Cape Town. [Online]. Available http://www.cssr.uct.ac.za. [2007, December 12].

Natu, S.A. & Daga, S.R. 2007. Antiretroviral therapy in children: Indian experience. *Indian Paediatrics.* 44(5): 339-343.

Newell, M.-L., Coovadia, H. & Cortico-Borja, M. 2004. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*. 364:1236-1243.

News24. 2007. SA launches R25bn Aids plan. [Online] Available: http://www.news24.com/News24/South_Africa/Aids_Focus/0,,2-7-659_2083450,00.html. [2007, March 14].

Nicholson, O. et al. 2005. HIV treatment-related knowledge and self-efficacy among caregivers of HIV-infected children. *Patient Education and Counseling*. 61(3):405-410.

Nyandiko, W.M. et al. 2006. Outcomes of HIV-Infected Orphaned and Non-Orphaned Children on Antiretroviral Therapy in Western Kenya. *Journal of Acquired Immune Deficiency Syndrome*. 43: 418-425.

O'Brien, D. et al 2006. Outcomes of Children on HAART in Médecins Sans Frontières Programs.[Abstract]. 16th International AIDS Conference. 16-18 August, Toronto, Canada. [Online] Available: http://www.msf.ca/aids2006/abstracts.html. [2007, March 26]

Olley, B.O. 2004a. Predictors of major depression in recently diagnosed patients with HIV/AIDS in South Africa. *AIDS Patient Care and STDS.* 18(8): 481-487.

Olley, B.O., Seedat, S. & Stein, DJ. 2004b. Psychopathology and coping in recently diagnosed HIV/AIDS patients. South African Medical Journal. 94(9): 720, 722.

Orrell, C. et al. 2003. Adherence is not a barrier to successful antiretroviral therapy in South Africa. *AIDS*. 17(9): 1369-1375.

Orrell, C. 2005. Antiretroviral adherence in a resource-poor setting. *Current HIV/AIDS Report.*2(4): 171-176.

Osler, M. 2007. National Health ARV statistics reporting format. [Personal communication, 9 August.] Cape Town. (Unpublished).

Ostrop, N.J., Hallett, K.A., & Gill, M.J. 2000. Long-term patient adherence to antiretroviral therapy. *The Annals of Pharmacotherapy*. 34(6): 703-709.

Oyugi, J.H. et al. 2004. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *Journal of Acquired Immune Deficiency Syndrome*. 36(5): 1100-1102.

Paediatric European Network for Treatment of AIDS (PENTA) 1998. HIV-1 viral load and CD4 cell count in untreated children with vertically acquired asymptomatic or mild disease. *AIDS*.12(4): F1-F8.

Palumbo, P. et al. 1995. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *Journal of Paediatrics.* 126: 592-595.

Parsons, G.N. et al. 2006. Multidisciplinary, inpatient directly observed therapy for HIV-1–Infected children and adolescents failing HAART: A Retrospective Study. *AIDS Patient Care and STDS*. 20 (4): 275-284.

Patterson, D. et al. 2000. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine*. 133: 21-30.

Pekovic, V. et al. 1998. Comparison of three composite compliance indices in a trial of self-administered preventative therapy for tuberculosis in HIV-infected Ugandan adults. *Journal of Clinical Epidemiology*. 51: 597-607.

Pensi, T. 2007. Fixed dose combination of Lamivudine, Stavudine and Nevirapine in the treatment of paediatric HIV infection: A preliminary report. *Indian Paediatrics*. 44(7): 519-521.

Paediatric European Network for Treatment of AIDS. (PENTA) 2004. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS.* 18: 237-245.

Pontali, E., Feasi, M. & Toscanini, E. 2001. Adherence to combination antiretroviral treatment in children. *HIV Clinical Trials*. 2: 466-473.

Pontali, E. 2005. Facilitating Adherence to Highly Active Antiretroviral Therapy in Children with HIV Infection: What are the issues and what can be done? *Paediatric Drugs*. 7(3): 137-149.

Pugatch, D. et al 2002. HIV Risk Behaviors in Adolescent and Young Adult Substance Users Undergoing Treatment. *Journal of HIV/AIDS Prevention & Education for Adolescents & Children.* 4(4): 43-54.

Puthanakit, T. et al. 2005a. Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program. *Clinical Infectious Diseases Journal*. 41(1): 100-107.

Puthanakit, T. et al. 2005b. Immune reconstitution syndrome due to bacillus Calmette-Guerin after initiation of antiretroviral therapy in children with HIV infection. *Clinical Infectious Diseases Journal*. 41(7): 1049-1052.

Radloff, L.S. 1977. The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1: 385-401.

Radloff, L.S. & Locke, B. 1986. The community mental health assessment survey and CES-D Scale. In Community surveys of psychiatric disorders. Weismann,M, Meyers,J. & Ross,C., Eds. New Brunswick, NJ: Rutgers University Press . 177-187.

Raiten, D., Grinspoon, S. & Arpadi, S. 2005. Nutritional considerations in the use of ART in resource-limited settings. Consultation on Nutrition and HIV/AIDS in Africa: Evidence, lessons and recommendations for action. [Online].Available: http: //www.who.int/nutrition/topics/Paper%20Number%206%20-%20Nutritional%20-%20ART.pdf. [2006, April 24].

Ramos, J.T. 2003. High Prevalence of Metabolic Abnormalities in HIV-infected Children Treated with HAART. [Abstract]. *10th Conference on Retrovirus Opportunistic Infections. 10-14 February*, Boston, Massachusetts.

Reddi A. et al. 2007. Preliminary Outcomes of a paediatric highly active antiretroviral therapy cohort from Kwa-Zulu Natal, South Africa. *BioMed Central Paediatrics.* 7 (13): [Online].Available: http://www.biomedcentral.com/1471-2431/7/13

Reddington, C. et al 2000. Adherence to medication regimens among children with human immunodeficiency virus infection. *The Paediatric Infectious Disease Journal.* 19(12): 1148-1153.

Ren, Y. et al. 2007. High prevalence of subtherapeutic plasma concentrations of Efavirenz in children. *Journal of Acquired Immune Deficiency Syndromes*. 45(2): 133-136.

Richardson, J. et al. 2001. Experience and covariates of depressive symptoms in infected women: *Social Work in Health Care*. 32: 93-111.

Roberts, G.M. et al. 2004. Non-adherence with paediatric human immunodeficiency virus therapy as medical neglect. *Paediatrics*. 114(3): e346-e353.

Rollins, N. et al. 2007. Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening**.** *AIDS.* 21(10):1341-1347.

Sackett, D.L. et al 1975. Randomized clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet*.1: 1205-1207.

Sarason, I.G. et al. 1983. Assessing social support: The Social Support Questionnaire. *Journal of Personality and Social Psychology*. 44: 127-129.

Schrimshaw, E.W. 2003. Relationship-specific unsupportive social interactions and depressive symptoms among women living with HIV/AIDS: Direct and moderating effects. *Journal of Behavioural Medicine*. 26: 297-313.

Schulberg, H.C. et al. 1985. Assessing depression in primary medical and psychiatric practices. *Archives of General Psychiatry.* 42: 1164-1170.

Secretary General of the Organisation of the African Union. 1990. African Charter on the Rights and Welfare of the Child. [Online] Available: http://www1.umn.edu/humanrts/africa/afchild.htm. [2006, March 26].

Secretary-General of the United Nations. 1989. Convention on the Rights of the Child. General Assembly resolution 44/25. [Online] Available: http://www.unhchr.ch/html/menu3/b/k2crc.htm. [2004, February, 12]

Shah, C.A. 2007. Adherence to high activity antiretroviral therapy (HAART) in paediatric patients infected with HIV: Issues and interventions. *The Indian Journal of Paediatrics*. 74(1): 55-60.

Sharland, M. et.al. 2004. PENTA guidelines for the use of antiretroviral therapy. *HIV Medicine.* 3, (3): 215-226.

Sherbourne, C.D. & Stewart, A.L. 1991. The MOS social support survey. *Social Science and Medicine*. 32: 705-714.

Shingadia, D. et al 2000. Gastronomy tube insertion for improvement of adherence to highly active antiretroviral therapy in paediatric patients with human immunodeficiency virus. *Paediatrics*. 105(6):e80. [Online] Available: http://www.pediatrics.org/cgi/content/full/105/6/e80 [2008, February 15].

Shungking, M. & Zampoli, M. 2005. Antiretroviral Roll-out in South Africa: Where do the children feature? Save the Children Sweden & Children's Institute, University of Cape Town. [Online] Available: http://www.ci.org.za/depts/ci/pubs/pdf/rights/facts/Save_the_Children_ARV_FINAL.pdf

Simoni, J. & Ng, M. 2000. Trauma, coping and depression among women with HIV/AIDS in New York City. *AIDS Care*. 12: 567-580.

Simoni, J.M. 2003. Antiretroviral Adherence Interventions: A Review of Current Literature and Ongoing Studies. *Topics in HIV Medicine*. 11(6):185-198. 2003.

Simoni, J. M. et al. 2005. Enhancing Antiretroviral Adherence: A review of published reports of randomized controlled trials and on-going NIH Funded research. In. *Best practices in the behavioral management of chronic disease*. Vol. 11: Other medical disorders. J. Trafton & W. Gordon, Eds. Los Altos, California: Institute for Brain Potential. 70-95.

Simoni, J.M. et al. 2007. Adherence to antiretroviral therapy for paediatric HIV Infection: a qualitative systematic review with recommendations for research and clinical management. *Paediatrics* 119(6): e1371-e1383.

Sirisanthana, T. & Sirisanthana, V. 2005. Immune reconstitution syndrome due to bacillus Calmette-Guerin after initiation of antiretroviral therapy in children with HIV infection. *Clinical Infectious Diseases*. 41(7): 1049-1052.

Sorensen, S.J. et al. 2002. Gender-related factors influencing medication and clinic visit adherence in HIV/AIDS patients. [Abstract] XIV International AIDS Conference. 7-12 July, Barcelona, Spain. Available: http://gateway.nlm.nih.gov/MeetingAbstracts/102254422.html. [2008, February 14].

Soza-Vento, RM. & Fritz, K. 2007. Parental Reports of Paediatric Adherence to Medication and Treatment in a clinical setting. [Abstract] *2nd International Conference on HIV Treatment Adherence.28-30 March*, Jersey City, NJ United States.

Starace, F. et al. 2006. Adherence to antiretroviral therapy: an empirical test of the information-motivation-behavioral skills model. *Health Psychology*. 25(2): 153-162.

Starr, S.E. et al.1999. Combination Therapy with Efavirenz, Nelfinavir, and Nucleoside Reverse-Transcriptase Inhibitors in children infected with Human Immunodeficiency Virus Type 1. *The New England Journal of Medicine.* 341(25): 1874-1881.

Statistics South Africa 2007. Mid-year population estimates, South Africa. [Online] Available: http://www.stastssa.gov/PublicationsHTML/P03022007/html/.[2008, 11 January].

Steele, R.G. et al. 2001. Adherence to antiretroviral therapy among HIV-positive children: examination of the role of caregiver health beliefs. AIDS Care 13(5): 617-629.

Steele, R.G. & Grauer, D. 2003. Adherence to Antiretroviral Therapy for Paediatric HIV Infection: Review of the Literature and Recommendations for Research. *Clinical Child and Family Psychology Review*. 6(1): 17-30.

Steiner, J.F. & Prochazka, A.V. 1997. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of Clinical Epidemiology*. 50(1): 105-116.

Stewart, R. & Loveday, M. 2005. Operational Plan: implementation of the antiretroviral therapy component Chapter 16. In *South African Health Review 2005.* P. Ijumba & P. Barron, Eds. Durban, South Africa. Health Systems Trust. 224-227.

Stone, V. E. 2000. Primary care of the patient with HIV/AIDS. *Infectious Disease Clinics of North America.* 14(4): 967-981.

Stone, V. E. et al. 2004. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *Journal of Acquired Immune Deficiency Syndrome*. 36(3): 808-816.

Temple, M. E., Koranyi, K. & Nahata, MC. 2001. The safety and antiviral effect of protease inhibitors in children. *Pharmacotherapy.* 21: 287-294.

The U.S. President's Emergency Plan for AIDS Relief.2006. Working in Partnership Annual Report. [Online] Available: http://www.usembassy.gov/southafrica/wwwfpepfar_reports20070601.pdf [2007, August 7]

Thorne, C., Newell, M.L. & Peckham, C.S. 2000. Disclosure of diagnosis and planning for the future in HIV-affected families in Europe. *Child Care Health and Development*. 26(1): 29-40.

Tuldra, A. et al. 2000. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndrome*. 25: 221-228.

Turner, B.J. & Hecht, F.M. 2001. Improving on a coin-toss to predict patient adherence to medications. Annals of Internal Medicine. 134: 1004-1006.

UNAIDS. 2006. *Global Facts and Figures*. [Online]. Available: http://data.unaids.org/pub/Epireport/2006/20061121_Epi_F5_Globalfacts_en.pdf. 1-12-2006. [2007, May 22].

UNICEF/WHO Technical Consultation.2004. *Improving Access to Appropriate Paediatric ARV Formulations*. [Online] Available: http://www.who.int/3by5/en/finalreport4Apr.pdf. [2004, December 3].

United Nations Children's Fund.2004. *Children on the brink. (A Joint Report).* [Online]. Available: http://www.unicef.org/publications/files/cob_layout6-013.pdf. [2006, August 11].

Urquhart, J. 1992. Ascertaining how much compliance is enough without patient antibiotic regimens. *Post Graduate Medical Journal*. 68(13): 49-59.

Van Dyke, R.B. et al. 2002. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Paediatrics*. 109(4): e61.

van Rossum, A.M., Fraaij, PL. & de Groot, R. 2002. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. *The Lancet Infectious Diseases*. 2: 93-102.

van Rossum, A.M. et al. 2002. Results of 2 Years of Treatment with Protease-Inhibitor-containing Antiretroviral Therapy in Dutch Children Infected with Human Immunodeficiency Virus Type 1. Clinical Infectious Diseases. 34: 1008-1016.

Verweel, G. et al. 2002. Treatment with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children is associated with a sustained effect on growth. *Paediatrics.* 109(2): 304.

Verweel, G. et al. 2006. Initiating highly active antiretroviral therapy in human immunodeficiency virus type 1-infected children in Europe and the United States: comparing clinical practice to guidelines and literature evidence. *The Paediatric Infectious Disease Journal*. 25(11): 987-994.

Violari, A. et al. 2007. Antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study. [Abstract] 4th IAS Conference., 22-25 July, Sydney, Australia. Available: http://www.ias2007.org/abstract.aspx?elementId=200705557 [2007, August 8].

Vreeman, R. et al. 2007. The measurement of paediatric adherence to antiretroviral therapy: a systematic review. [Abstract] 4th IAS Conference., 22-25 July, Sydney, Australia. Available: http://www.ias2007.org/abstract.aspx?elementId=200702224. [2007, August 8].

Vrijens, B., Gross, R. & Urquhart, J. 2005. The Odds that Clinically Unrecognized Poor or Partial Adherence Confuses Population Pharmacokinetic/Pharmacodynamic Analyses. *Basic & Clinical Pharmacology & Toxicology.* 96: 225-227.

Wagner. G.J. & Rabkin, J.G. 2000. Measuring medication adherence: are missed doses reported more accurately than perfect adherence. *AIDS Care*. 12(4): 405-408.

Walsh, J., Mandalia, S. & Gazzard, B. 2002. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS.* 16: 269-277.

Watson, D. & Farley, J. 1999. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *The Paediatric Infectious Disease Journal*. 18(8): 682-689.

Wedekink, C.A. & Pugnatch, D. 2001. Lipodystrophy syndrome in children infected with human immunodeficiency virus. *Pharmacotherapy.* 21: 861-866.

Weiser, S. et.al. 2003. Barriers to Antiretroviral adherence for Patients living with HIV infection and AIDS in Botswana. *Journal of Acquired Immune Deficiency Syndrome.* 34(3): 281-288.

Western Cape Department of Health. 2006. The Western Cape Antiretroviral Programme: Monitoring Report. June 2006. Cape Town: Provincial Government of the Western Cape. (Unpublished).

Wiener, L.S., Vasquez, M.P. & Battles, H.B. 2001. Fathering a child living with HIV/AIDS: Psychosocial adjustment and parenting stress. *Journal of Paediatric Psychology*. 26: 353-358.

Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children. 2005. *Guidelines for the use of antiretroviral agents in paediatric HIV infection.* [Online] Available: http://AIDSinfo.nih.gov. 24-3-2005. [2005, April 10].

World Health Organization. 2003a. *Treating 3 million by 2005: making it happen*. [Online] Available: http://www.who.int/mediacentre/news/releases/2003/pr89/en/print.html. [2007, June 6].

World Health Organization. 2003b. *Adherence to long term therapies: Evidence for Action*. [Online] Available: http://www.who.int/chronic_conditions/en/adherence_introduction.pdf. [2003, December 13].

World Health Organization 2003c. *South Africa: A novel approach to improving adherence to TB treatment. Essential Drugs Monitor (33).* World Health Organization, Geneva, 33. [Online] Available: http://mednet2.who.int/edmonitor/33/mon33.html. [2004, June 20].

World Health Organization 2004. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva*. [Online] Available: http://www.who.int/hiv/pub/mtct/en/arvdrugswomenguidelinesfinal.pdf. [2006, August 20]

World Health Organization. 2006a. *Progress to Global Access to Antiretroviral Therapy. A report on "3 x 5" and beyond.* [Online]. Available: http://www.who.int/hiv/fullreport_en_highres.pdf. 1-3-2006. [2006, April 21].

World Health Organization.2006b. *Global Access to HIV Therapy Tripled in Past Two Years, But Significant Challenges Remain: 1.3 Million People Now Receiving Treatment in Low- and Middle-income Countries; Sub-Saharan Africa Leads in Treatment Scale-up.* [Online]. Available: http://www.who.int/hiv/mediacentre/mews57/en/print.html. 2006. [2006, April 24].

World Health Organization 2006c. *ARV drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-Limited Settings: Treatment Guidelines*. [Online]. Available: http://www.who.int/hiv/pub/mtct/pmtct/en/. [2007, January 11]

World Health Organization. 2006d. *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach.* [Online]. Available: http://www.who.int/hiv/pub/guidelines/art/en/ Geneva. [2007, January 12]

World Health Organization. 2007. Standard deviation of anthropometric z-scores as a data quality assessment using the 2006 WHO growth standards: a cross country analysis. *Bulletin of the World Health Organization*. 85(6): 441-448.

World Health Organization. 2008. *Task shifting: rational redistribution of tasks among health workforce teams.* [Online]. Available: http://www.who.int/entity/healthsystems/TTR-TaskShifting.pdf. [2008, January 28].

Wrubel, J. et al. 2005. Paediatric adherence: perspectives of mothers of children with HIV. *Social Science & Medicine.* 61: 2423-2433.

# APPENDICES

# Appendix 1: Ethics Approval

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
E53 Room 44.1, Old Main Building Groote
Schuur Hospital, Observatory, 7925
Queries : Xolile Fula
Tel : (021) 406-6492 Fax: 406-6411
E-mail : Xfula@curie.uct.ac.za

30 August 2004

REC REF: 256/2004

Ms DC Michaels
c/o Prof L London
Public health & Family Medicine

Dear Ms Michaels

FACTORS INFLUENCING HAART ADHERENCE IN HIV-INFECTED CHILDREN AGED 0-6YEARS IN A RESOURCE-POOR SETTING, CAPE TOWN, SOUTH AFRICA

*Thank you for submitting your study to the Research Ethics Committee for review.*

*It is a pleasure to inform you that the Ethics Committee has* ***formally approved*** *the above-mentioned study on the 30th August 2004.*

*Your comments to our queries are noted with thanks.*

Please quote the REC. REF in all your correspondence

Yours sincerely

PROF. T. ZAMOW
CHAIRPERSON

## Appendix 2: Letter from RXH

Annexure 3


**UNIVERSITY OF CAPE TOWN**

**SCHOOL OF CHILD & ADOLESCENT HEALTH**

DIVISION: PAEDIATRIC MEDICINE
RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL
KLIPFONTEIN ROAD
RONDEBOSCH
7700

TEL: +27 21 658 5319/5242
FAX: +27 21 689 1287


12 May 2004

Ms Desiree Michaels
Department of Public Health and Family Medicine
University of Cape Town

Dear Desiree

**PhD Research Proposal: Promoting adherence to HAART in children < 6 Years in a resource-poor setting, South Africa**

Your proposed research project is relevant and timely, as it will address issues that are central to the success of antiretroviral therapy for children in South Africa. The Infectious Diseases Service at Red Cross Children's Hospital is sufficiently developed to support this project. Therefore we will provide you with access to our patient cohort and the support needed to undertake your project.

Yours sincerely

Dr Brian Eley
Infectious Diseases Service

# Appendix 3: Consent Form (English)

I understand that I have been asked to take part in this study because my child has been started on antiretroviral treatment for HIV infection. The researcher has explained to me that this study is aimed at understanding what factors affect children's ability to take the antiretroviral medication.

The researchers have explained that I will be completing two administered questionnaires which will last approximately 45 minutes to an hour approximately one month after my child started the treatment. Subsequent questionnaires regarding the medication will be administered at the 3month and 6 month visits.

I understand that my child's clinic records will be used to obtain information about their clinical and virological status.

I understand that the specific answers I give will not be given to the doctors or the health staff that provide me with the treatment and there will be no change with regard to the treatment I receive.

I understand that I may be invited to participate in a focus group discussion with other parents to discuss issues relating to children on antiretroviral treatment.

The researchers have explained that I am not obliged to take part in this study and if I refuse to take part, it will not affect the service I receive at the hospital.

I agree to take part in this study and give permission for the researchers to access my child's medical folder.

Signature: _____
Date: _____

I am / **am not** willing to participate in a focus group discussion should I be invited to do so.

Signature: _____

Date: _____

Date of Focus Group: _____

## Appendix 4 : Enrolment Form

Enrolment Number: __/__/__ Date of Enrolment: __/__/____Completed by: _____

Patient Folder No: _____ ARV Start date: __/__/____

Name & Surname of Child: _____

D.OB: __/__/____ (dd/mm/yyyy) Gender: M / F (circle)

**Caregiver Contact Details:**

Name and Surname: _____ [Print]

Relationship to the Child: _____

Address: _____

_____

Tel No: _____ (h) Cell: _ _ _ _ _ _ _ _ _ _ No telephone/s

**Ask Caregiver:**

1. Has the child attended the ID clinic prior to ARV treatment? Yes__No_
*(Ingaba umntwana uhambe lekliniki phambi kokuba aqalise unyango lwentsholongwane)*

2. If yes, since when (mm/yyyy)? (Ukuba ewe, uqale nini) _____
3. How did you get access to this ID clinic at the hospital?
*(Ingaba wangena njani kule kliniki ilapha esibedlele)*

1= referred by community clinic

*(Ndathunyelwa yikliniki yase kuhlaleni)*

2= referred by hospital after child was hospitalised

*(Ndathunyelwa sisibhedlele emva kokuba umntwana wayelalisiwe*)

3= Other [specify] (*Enye – chaza*)_____

4. When was the last time this child was sick? (days/ weeks or months) _____
*(Ugqibele nini umntwana ukugula)*

5. What was wrong with the child? _____
*(Yayi yintoni ingxaki yomntwana)*

6. Does the child have any health problems today? Yes __ No__ [If no, skip to 8]
*(Ingaba umntwana unengxa ngokwempilo namhlanje)*

7. If yes, what is wrong? _____
*(Ukuba ewe, yintoni ingxaki)*

8. Is the child currently being given any other medication? Yes__No___
*(Ingaba umntwana unikwa amanye amayeza angamanye)*

9. If yes, specify (condition & medication) _____
*(Ukuiba ewe, chaza – imeko namayeza)*

_____

10. What, in your opinion, is the reason for the child starting Antiretroviral treatment?

(*Yintoni, ngokokwakho, isizathu sokuba umntwana aqalise olunyango lukaGawulayo)*

_____

From whom did you get information about the ARV treatment?

(Ingaba walufumana phi ulwazi malunga nalamachiza entsholongwane kaGawulayo)

1= counsellor *(Umcebisi)*

2= nurse *(Umongikazi)*

3= doctor *(uGqirha)*

4= social worker *(UnoNtlalo-Ntle)*

5= 1,2 + 3

9= Don't remember *(Andikhumbuli)*

11. What do you remember about what they told you about the treatment for the child? *(Yintoni oyikhumbulayo malunga nowakuxelelwayo ngolunyango lomntwana)*

_____

_____

**For Office Use Only**

**Medical History**

**Information to be obtained from patient folder]**

13. Has the child attended the ID clinic prior to ARV treatment? Yes__No__
14. If yes, since when (mm/yyyy)? _____
15. If not, was the child referred for ARVs? Yes __ No__ N/A___
16. If yes, who referred (institution/clinic)? _____
17. Is the child currently on TB treatment? Yes __ No__
18. If yes, since when? _____
19. Is the child currently on Cotrimoxazole/Bactrim? Yes __ No ___
20. Was the child exposed to ARVs through PMTCT programme? Yes ___ No ___
21. If yes, (specify) 1= AZT
    2= NVP
    3= Combination therapy
    9=Don't Know
22. Last hospitalization date: __/____ (mm/yyyy)
23. Reason for hospitalization: _____
24. Date of Completion of screening questionnaire:__/__/____ (dd/mm/yyyy)
25. Medical Reason for commencing treatment (as noted on screening questionnaire)
    _____
    _____
26. Other significant medical problems
    a. HIV related:_____
    b. Non HIV related:_____
27. 22. Clinical stage on Starting Haart:_____

**Baseline Data**

| | Baseline |
|---|---|
| CD4 Count / % | |
| Viral Load | |
| Weight | |
| Height | |

| **HAART Regimen:** |
|---|
| |
| |
| |
| |

| Other Drugs | Reason for prescription |
|---|---|
| | |
| | |
| | |

**Enrolment Procedure Checklist**

1. Obtain Consent ……..……..آ
2. Complete Enrolment log…….…..آ
3. Complete this enrolment Form…….….آ

# Appendix 5: Standard Operating Procedures

## Objective of the Study

This is a prospective cohort study to determine how four different measures of adherence approximates immunological and virological markers and explore factors impacting on adherence to HAART in children under 6 years of age.

## Eligibility

All children under 6 years of age initiating HAART between the period October 2004 and October 2005 are eligible for enrolment into the study.
(Note: All children

*Exclusion criteria*
Children who are in long term residential care, at a children's home are not eligible.

## Study Procedures

This study will be conducted along side the routine ARV service provided at the Red Cross Children's War Memorial Hospital. No additional phlebotomy procedures will be conducted for the purposes of this study. Immunological and virological results will be obtained from the patient folder or hospital records.

## Enrolment

Patients will be identified at the Tuesday and Friday Infectious Diseases outpatient clinics.

## Tuesday Morning Clinic

Tuesday clinics are held in S20 and the sisters-in-charge are Brenda Joshua (for PAWC) and Desireé Jansen (for research).

The designated person for the Adherence study will identify patients by perusing patient folders in the record clerk's office. The inclusion of a 'screening questionnaire' form in the patient folder indicates a candidate for ARVs or a patient on ARVs. Patients who are indicated to commence ARVs or who are making their two week visit appointment will be identified at this stage for enrolment.

*Patients at 2 week post ARV initiation visit.*
These patients will be identified and approached by the researcher for consent to participate in the study.
Patients indicated for work up to initiate ARVs can only be confirmed after consultation with the doctors. The appointment dates of the next visit of these patients should be obtained for recruitment at the next visit if necessary.

**Friday morning Clinic**

Friday clinics are held in S19 and the research nurse co-ordinator is Sr Patricia Appolles.
The names of eligible patients for recruitment at this clinic will be obtained prior to the clinic being held on a Friday. Attendance of these patients will be confirmed on the day of the clinic and relevant patients approached for enrolment into the study by the researcher.

**Enrolment Procedures**
(To be conducted within 2-3 weeks of initiation on HAART)

1. The researcher will explain the purpose of the study and the procedures to be followed during the follow-up.
2. Consent will be obtained. The patient will sign a consent form and they will be given a copy of the consent form.
3. Once consent has been signed, an enrolment form will be completed.
4. Should the patient have been in consultation with the doctor already, their next clinic appointment date will be obtained directly from he patient (recorded on the appointment card). Should the patient still require seeing the doctor the next appointment date will be obtained after the clinic session from the sister-in-charge who will access the appointment book for this information.
5. All clinical information to be recorded on the enrolment form will be obtained from the patient folder subsequent to the clinic. (Note: the folder may not be retained by the researcher thereby hampering the patient's flow in the referral system – pharmacy etc.). The folder will be requested from records via Srs P. Appolles or D. Jansen if necessary.

**Document Checklist for this visit:**

1. Consent Form……. __
2. Complete Enrolment Log details…… __
3. Enrolment Form…….. __

**Visit 1 after enrolment (1 month after initiating ARVs)**

*Socio-demographic and treatment Baseline Data Collection*
(To be conducted within 4-6 weeks after initiation on HAART)

*The following documents/procedures to be completed during patient visit.*

4. Baseline questionnaire (not to be conducted by the same person doing the self-reported adherence questionnaire).
5. Prospective Study case report form.
6. Self –Report Adherence Questionnaire
7. Pill Count/ Medication measure.
8. Record whether the patient's appointment visit is on time or not. (Note: An 'on-time appointment is defined as 'on time' 7 days around the given date but no longer than 3 days after the given date.)

The following procedures to be completed by researcher subsequent to visit.

1. Check patient pharmacy refill computerised record for quantities and dates of prescriptions filled.
2. Note whether pharmacy prescriptions were collected 'on-time'

**Document Checklist for this visit:**

1. Baseline questionnaire …… __
2. Self-reported adherence questionnaire …….. __
3. Pill count/medicine measure results …….. __
4. Follow-up visit Case Report Form ……. __
5. Appointment schedule noted ……. __

**Visit at 3 months**

*The following documents/procedures to be completed during patient visit.*

1. Prospective Study case report form.
2. Self –Report Adherence Questionnaire
3. Pill Count/ Medication measure.
4. Record whether the patient's appointment visit is on time or not. (Note: An 'on-time appointment is defined as 'on time' 7 days around the given date but no longer than 3 days after the given date.)

*The following procedures to be completed by researcher subsequent to visit.*

1. Check patient pharmacy refill (computerised record or prescription chart in patient folder) for quantities and dates of prescriptions filled.
2. Note whether pharmacy prescriptions were collected 'on-time' based on appointment and collection dates.
3. Enter information on data capture form

**Document Checklist for this visit:**

1. Prospective enrolment form…… __
2. Self-reported adherence questionnaire …….. __
3. Pill count/medicine measure results …….. __
4. Follow-up visit Case Report Form ……. __
5. Appointment schedule noted ……. __

**Visit at 6 months**

Repeat all procedures as for visit at 3 months.

*The following procedures to be completed by researcher subsequent to visit.*

1. Check patient pharmacy refill (computerised record or prescription chart in patient folder) for quantities and dates of prescriptions filled.
2. Note whether pharmacy prescriptions were collected 'on-time' based on appointment and collection dates.
3. Obtain viral load results for 6 month visit
4. Enter information on data capture form

**Document Checklist for this visit:**

1. Prospective enrolment form…… __
2. Self-reported adherence questionnaire …….. __
3. Pill count/medicine measure results …….. __
4. Follow-up visit Case Report Form ….…… __
5. Appointment schedule noted ……. __

Procedures for quality control

1. Complete the Quality control sheet to identify missing data is captured.
2. Request patient folders through sister-in-charge to obtain any missing data.
3. Prepare folders and data capture sheets for researcher to abstract information from patient folders.

## Appendix 6: Case Report Form

Enrol No:_/_/_
Visit No. ____
Gender: M / F (circle)
ARV Start date: __/__/____
Visit Date: __/__/___
Next Visit Date: _____ CRF Completed by:_____

| | Baseline | 6 mths | 12mths | 18mths |
|---|---|---|---|---|
| CD4 | | | | |
| Viral Load | | | | |

**HAART Regimen**
**1.**_____
**2.**_____
**3.**_____

| Checklist | Date Done | Yes√ No X | (Comment) |
|---|---|---|---|
| 1. Returned unused medicines | | | |
| 2. Kept appointment as scheduled | | | |
| 3. Primary caregiver accompanied child | | | |
| 4.Self-reported adherence questionnaire completed (1, 3,6,) | | | |
| 5. Pill Count/meds measurement done (1,3,6,) | | | |
| 6. Pharmacy refill record checked (1,3,6 months) | | | |

**Health Status**

**Obtain information from folder**
7. Height: _____ 8. Weight: _____
9. TB Rx? Yes __ No__ 10. Bactrim? Yes __ No ___
11. Other drugs? Yes__ No___
12. If yes, give reason for prescription_____

**Ask Caregiver:**

13. Has the child been in hospital since the last visit? Yes___ No___
*(Ingaba umntwana wakhe walaliswa esibhedlele emva kotyelelo olugqithileyo)*
14. If yes, No. of admissions?
*Ukaba ewe, ulwamkelo?*
15. Total duration of all hospital admissions (in days) _____
*( (Ixesha elingakanani)*_____
16. Does the **caregiver** have specific complaints about the child's health? Yes _No__
*(Ingaba umongi unezikhalazo anazo malunga nemplilo yomntwana)*

17. If yes, specify
*(Ukuba ewe, chaza)*

_____

18. Has the child experienced any of the following since the last visit?Yes_ No__N/S__
*(Ingaba umntwana wakhe wanenye yezingxaki zilandelayo emva kotyelelo lokugqibela)*

1= headaches *(Intloko)*
2= vomiting after taking medicine *(Ukugaba emva kokuthatha amayeza)*
3= Rash *(Amaqhakuva amaninzi amacinci emzimbeni)*
4= abdominal pain *(Intluku zamanqa)*
5=fever [in opinion of caregiver] *(Umkhuhlane)*
6= diarrhoea *(Ukuhambisa)*
7= listlessness [having no energy, sleeping a lot] *(Ukungabi namdla)*
9=Other [specify] *(Enye- Chaza)*

_____

**Appetite and Food security**

19.Have there been any changes in the child's appetite (increase or decrease ); does the
(Ingaba kukhe kwakho umahluko emntwanani malunga nomdla wokutya [ unyukile okanye uhlile]: inagaba umntwana utya ukutya kwesiqhelo/ kakhulu okanye kancinci kunesiqgelo)

child eat regular meals / more or less than usual?

_____
_____

20. In your opinion, has there been sufficient food to satisfy the child's appetite? (What does the child eat mostly?) Is there sufficient food for the household?
(Ngokwezimvo zakho, ingaba bekukho ukutya okwaneleyo ukwanelisa umdla womntwana? utya ntoni umntwana ixesha elininzi? Ingaba kukho ukutya okwaneleyo ukwanzela ikhaya lonkwe)

_____
_____

**Social**

*(Ezentlalo)*
21. Any changes in the household routine or child-minding arrangements since the last visit? Yes ____ No___
*(Ingaba akukho tshintsho kwizicwangciso zekhaya okanye ukucinga komntwana ukususela kutyelelo lokugqibela)*
21. If yes, specify *(Ukuba ewe, chaza)*

_____
_____

22. Any significant family events occur since the last visit?
*(Ingaba akukho ziganeko zekhaya zibablulekileyo ezithe zenzeka emva kondwendwelo lokugqibela)*

1= funerals, *(Umncwabo)*
2=hospitalizations, *(Ulalo esibhedlele)*
3=illness of primary caregiver, *(Ukugula kukamongi)*
4=illness of sibling *(Ukugula kwenzala)*
5=illness of other family member whom caregiver had to look after
*(Ukugula kwelinye ilungu lekhaya ebeliphantsi komongi)*
6=retrenchments *(Ukuphelelwa ngumsebenzi)*
7= No change in circumstances *(Akukho zinguqu)*
8= refused to answer *(Walile ukuphendula)*
9=Other [specify] *(Enye – chaza)*

_____
_____

CES-D Score /____/ MOS Score/_____/

**General Comments**

_____
_____
_____

## Appendix 7: Medication Measure Assessment Form

| Enrolment No: ____ | ARV Start Date:____ |
|---|---|

**Dispensing Record**

| | Medicine | Dose | Times/day | Date Commenced | Date Stopped/changed |
|---|---|---|---|---|---|
| 1. | | | | | |
| 2 | | | | | |
| 3. | | | | | |
| 4. | | | | | |
| 5. | | | | | |

**Adherence Record:**

**Drug 1(AZT,d4T or ABC)**

| Medicine | Adherence | Month 0 | Month 1 | Month 3 | Month 6 |
|---|---|---|---|---|---|
| | Assessment Date (dd/mm/yyyy) | | | | |
| | Assessed by:[Print] | | | | |
| | Dispensed (ml or tabs) | | | | |
| | Returned Meds | | | | |
| | Expected usage: | | | | |
| | Actual usage | | | | |
| | %Adherence | | | | |

**Drug 2 (3TC of ddI)**

| Medicine | Adherence | Month 0 | Month 1 | Month 3 | Month 6 |
|---|---|---|---|---|---|
| | Assessment Date (dd/mm/yyyy) | | | | |
| | Assessed by:[Print] | | | | |
| | Dispensed (ml or tabs) | | | | |
| | Returned Meds | | | | |
| | Expected usage: | | | | |
| | Actual usage | | | | |
| | %Adherence | | | | |

**Drug 3(NVP,EFV,RTV,KLT)**

| Medicine | Adherence | Month 0 | Month 1 | Month 3 | Month 6 |
|---|---|---|---|---|---|
| | Assessment Date (dd/mm/yyyy) | | | | |
| | Assessed by:[Print] | | | | |
| | Dispensed (ml or tabs) | | | | |
| | Returned Meds | | | | |
| | Expected usage: | | | | |
| | Actual usage | | | | |
| | %Adherence | | | | |

# Appendix 8: Hypothesis Statements

| Variable | Stata variable name | Coding | A priori Hypothesis |
|---|---|---|---|
| **Child Characteristics** | | | |
| Age (in months) | **Agemo (continuous)** | | Inverse correlation between adherence and age |
| gender | **Gender (Categorical)** | Male | Boys more likely to be adherent (Boys are more valued than girls) if dependent on caregiver (perceived as more sick? Or are more valued) |
| Recent sickness | **Lastsick Ordinal** | Months | Those reporting sickness within one month of arv start are more likely to be adherent |
| Report health problem at 1st visit | **Healthprob binary** | Yes / No | Those reporting a health problem at enrolment are more likely to be adherent |
| ID clinic attendance prior to arv start | **Idattend binary** | Y/N | Those reporting "Yes" were more likely to be adherent |
| Period between first visit to IDC and ARV start | **since (days/ months)** | Calculate interval between "arvstart" and "idsince" | Those with the longest interval between "arvstart" and "idsince" are more likely to be adherent |
| TB Rx at enrolment | **Currenttbrx** | Y/N | Those who do not report having TB at enrolment are more likely to be adherent |
| WHO clinical staging | **Staging Categorical** | 1,2 & 3,4, | Those in stages 3 and 4 are more likely to be adherent than those in stages 1,2 |
| Period between last hospitalization date and ARV initiation | **dayslasthosp** | Days / Months | Those with the shortest interval[within 1 month] between "arvstart" and "lasthosp" date are more likely to be adherent |
| Otherdrugs other than bactrim and arvs at enrolment | **Otherdrug1, Otherdrug2, otherdrug3** | Combine three variables and transform to Yes/No | Those who do not report 'any other drugs' are more likely to be adherent |
| z-scores | **HAZ, WAZ,WHZ** | separate nutritional indicators | Those with poor nutritional indicators, more likely to be more sick, thus more adherent. |
| **Caregiver Characteristics** | | | |
| Caregiver Relationship to child | **Reltochild (categorical) Recode to (Biomom Y/N)** | 1= Biological mother<br>2=Grandmother<br>3=aunt<br>4=Foster mother<br>5=Other<br>6=Grandfather | Biological parents more likely to be adherent. |
| Mom went through PMTCT programme? | **PMTCT (binary)** | Y/N<br>*combine "N" and "Not sure"<br>1=Yes<br>2=No<br>97=N/A<br>98=Not entered<br>99=Don't know | Those who report not going through PMTCT are more likely to be adherent (those who respond yes – more likely to be in denial, thus less adherent) |
| Age | **C1howoldare** | Under20 | Those in the 20-30 age category are |

| Variable | Stata variable name | Coding | A priori Hypothesis |
|---|---|---|---|
| | **Categorical** | 20-30<br>31-40<br>41-50<br>51-60<br>60 and over | more likely to be biological parents and thus more adherent |
| Education | **C2higheststd categorical** | No schooling<br>Junior primary<br>Senior primary<br>Junior high<br>Senior high | Those with a senior high education are more likely to be adherent |
| Postschooltraining | **C3postschooltrain**<br>**Binary** | Y/N<br>1=Yes<br>2=No<br>97=N/A<br>98=Not entered<br>99=Don't Know | Post school train does not influence adherence |
| Employment status | **C6employmentstatus** | 1=Casual<br>2=Formal<br>3=Homebusiness<br>4=Unemployed | Those in the categories 4"unemployed" and 3"Homebusiness" are more likely to be adherent. |
| Fertility plans | **D7planningmore children** | 1=Yes<br>2=No<br>3=N/A<br>4=Not sure | Those in categories Yes (1) and Not sure (4) are more likely to be adherent |
| Depression | **CED-D scores** | 1.Categorize >15 (convention) and or<br>2.Establish threshold for cohort | Those who are depressed are more likely to have non-adherent children. |
| Know the names of ARVs | **Knownames** | Y /N | Those familiar with ARV names after 1 month, more likely to be adherent. |
| Marital status | **Marital status (Y/N) (married/living together)** | 1=single<br>2=widowed<br>3=divorced<br>4=Married<br>5=Living with Parner<br>6= Partner died | Those married or living with partner, more likely to have adherent children |
| **Socio-economic characteristics** | | | |
| Housing | **D1housing Categorical** | Formal<br>Informal | Those in "formal" are more likely to be adherent |
| Water | **D2water Categorical** | Inside tap<br>Outside tap | Those with "inside tap" are more likely to be adherent |
| Sanitation | **D3sanitation categorical** | Inside toilet<br>Outside pail<br>none | Those with "inside toilet are more likely to be adherent |
| Housing density | **D4children D5Adults continuous** | Combine two variables D4+d5 =housing density | Increased number of children and adults in household impacts negatively on adherence. |
| Any other household members known to be infected | **D9anyinfected (categorical)** | Yes/No/ Don't know | Those in households with known HIV infected members are more likely to be adherent |

| Variable | Stata variable name | Coding | A priori Hypothesis |
|---|---|---|---|
| Grants | **Grants** | **(Y/N)** | Those receiving grants more likely to be adherent. |
| Significant Life events | **LE** | 1=funerals<br>2=hospitalizations<br>3=illness of primary caregiver<br>4=illness of sibling<br>5=illness of other family member<br>6=retrenchments<br>7=No changes<br>8=refused to answer<br>9=Other | Those experiencing significant life events during follow-up, less likely to be adherent |
| Health Service Characteristics | | | |
| Who counseled at arvstart | **Whocounsel Counsellor vs. Doctor/nurse** | 1=counsellor<br>2=nurse<br>3=doctor<br>4=social worker<br>5=1,2,3 above<br>6=1,3 above<br>9=cannot remember Not sure | Those counseled by counsellors were more likely to be adherent. |
| Route of access to clinic | **Access (categorical)** | 1=community clinic<br>2=ward<br>3=other | Those who gain access via hospital ward are more likely to be adherent |
| Referred for ARVs only | **Referred (Binary)** | Y/ N+N/A | Those who were not specifically referred for ARVs (N+N/A) are more likely to be adherent |

## Appendix 9: Power and Sample Size Calculations

**Effect size conventions: small = .20 medium = .50 large = .80**

| Effect size | Alpha | Power | Sample size | Actual Power |
|---|---|---|---|---|
| 0.2 | 0.05 | .80 | 788 | 0.8006 |
| 0.2 | 0.05 | .70 | 620 | 0.7006 |
| 0.2 | 0.05 | .60 | 492 | 0.6002 |
| 0.2 | 0.05 | .50 | 388 | 0.5020 |
| 0.2 | 0.05 | .40 | 294 | 0.4010 |
| 0.2 | 0.05 | .30 | 208 | 0.3003 |

| Effect size | Alpha | Power | Sample size | Actual Power |
|---|---|---|---|---|
| 0.4 | 0.05 | .80 | 200 | 0.8036 |
| 0.4 | 0.05 | .70 | 158 | 0.7049 |
| 0.4 | 0.05 | .60 | 126 | 0.6055 |
| 0.4 | 0.05 | .50 | 98 | 0.5001 |

| Effect size | Alpha | Power | Sample size | Actual Power |
|---|---|---|---|---|
| 0.5 | 0.05 | .80 | 128 | 0.8015 |
| 0.5 | 0.05 | .70 | 102 | 0.7056 |
| 0.5 | 0.05 | .67 | 96 | 0.6788 |
| 0.5 | 0.05 | .60 | 82 | 0.6090 |
| 0.5 | 0.05 | .50 | 64 | 0.5036 |

| Effect size | Alpha | Power | Sample size | Actual Power |
|---|---|---|---|---|
| 0.8 | 0.05 | .95 | 128 | 0.8015 |
| 0.8 | 0.05 | .90 | 56 | 0.9050 |
| 0.8 | 0.05 | .80 | 42 | 0.7056 |
| 0.8 | 0.05 | .60 | 82 | 0.6090 |
| 0.8 | 0.05 | .50 | 28 | 0.5312 |

***Calculated using G*Power statistical software**

## Appendix 10: Baseline Questionnaire:

**This questionnaire must be administered within 2- 4wks of the patient starting ARV therapy.**

**PROCEDURE CHECKLIST:**

1. Complete Case Report Form for Visit 1 …….. أ
2. Complete this questionnaire. …… أ
3. Remind Caregiver to bring all medicine containers (medicine bottles and capsule pkts) at the next visit (1 month after starting ARV) ……. أ

**Interviewer Name:_____**
**Date of Interview**:_____ **Patient Folder number:** _____
**Patient Enrolment Number:__/__/__**
**Name of child**:_____
**Date of birth** (dd/mm/yyyy) __/__/_____ [NB. Only 6 yrs or younger]
**Gender**: boy □ girl □
**ARV start date**:_____

**NOTE:**
**A.1. Who is the primary caregiver of this child?[relationship] _____**
***(Ngubani oyena omelene nokunika umntwana amayeza)***
A.2. Who is mainly responsible for giving the medication?_____
***[If not the person being interviewed, stop interview and make arrangements to see the responsible person at a later stage]***

**Interview completed?** Yes□ No□
**If No, specify reason** _____
**Interviewee:** [Relationship to Child]_____

**B.1. Who responded to this questionnaire? [circle appropriate number below]**
*(Ngubani ophendula lemibuzo)*
1=Both biological parents *(ngabazali bobabini…*[skip to C]
2=biological mother *(ngumama)* ……..[skip to C]
3=biological father *(ngutata)* ……[skip to C]
4=grandmother *(ngumakhulu)*
5= Aunt *(ngu-anti)*
6= Foster parent *(ngumzali owonyuliweyo)*
9= Other [specify]*(enye – chaza)*_____
**B.2. If not the biological parent, is the caregiver a legal guardian? Yes□ No□**
(Ukuba *ayingomzali, ingaba umncedi ngumzali owonyulwe ngokomthetho)*

**B.3. If not the biological parent, where are the parents?**
*(Ukuba ayingobazali, baphi abazali)*
1=mother deceased
2=father deceased
3=mother living elsewhere (specify)_____
4=Other
5= not applicable [in the case of adoptive, foster parents]
9= don't know [abandoned child]

**C. Demographic Details**
***(Inkcukaca zakho)***

Caregiver Details
***(inkcukaca zomncedi)***

**C1. How old are you?**
*(Mingaphi iminyaka yakho)*
Under 20 □ 20-30 □ 31-40 □ 41-50 □ 51-60 60 and over □
**C.2.. What was the highest standard passed at school? _____**
*(Liliphi elona banga liphezulu oliphumeleleyo)*
**C.3. Do you have any post-school qualifications? Yes □ No□ If no, go to C.5.**
*(Unayo imfundo ephakamileyo)*
**C.4 If yes, specify_____**
**C.5. Marital Status (Isimo ngokomtshato):**

1=single (awutshatanga)

2=widowed *(umyeni watshaba)*

3= divorced *(nohlukana)*

4=Married *(utshatile)*

5=living with partner *(uhlala neqabane)*

6= partner died *(iqabane latshaba)*

**C.6. Employment status (Isimo ngokomsebenzi):**
1= Formal employment (umsebenzi osisigxina)
[specify occupation:_____]
2=Unemployed (wausebenzi)
3=Casual employment (umsebenzi wamaxesha)
4=home business (ishishini lasekhaya)[specify:eg. spaza shop_____

**C.7.Who provides financial support in the home [relationship**
tchild]?_____
*(Ngubani onika inxaso ngezemali ekhaya)*
1= Self
2= Spouse
3= Both
4= borders
5= Other (specify:_____)
9= Did not answer question

**C.8. Do you receive any grants? Yes □ No□ If No, go to D.**
*(Ingaba kukho imali kaRhulumente oyifumanayo)*

**C.9. Specify type of grant?**
*(Chaza uhlobo lwale mali)*
1= child care dependency grant *(imali yokonga abantwana)*
2= Old age pension *(Inkam-nkam)*
3= disability grant *(Imali yokukhobozeka)*
4= child maintenance support [from father] *(Imali yokonga umntwana evela kutata)*
9= Other *(Enye)* [specify *(chaza)*]

**D. Household**

**D.1 Type of housing *(Uhlobo lwendlu)*:** informal dwelling □
formal brick dwelling □
**D.2 Access to water** *(Ufikelelo emanzini)*: outside tap only □ inside taps □
**D.3 Inside Flush Toilet** (Indlu yangasese engaphakathi etsalwayo) □ Outside toilet *(engaphandle)* □
**D.4 How many people live in the home?** (specify: _____adults _____children)
*(Bangaphi abantu abadala nabantwana abahlala endlini)*
**D.5 How many siblings does [child's name] have? _____**
*(Bangaphi abantakwabo anabo)*
**D.6. How many siblings are HIV infected? _____**
*(Bangaphi abantakwabo abosuleleke yile ntsholongwane kaGawulayo)*
***D.7.* Are you planning to have any more children?** Yes □ No □ Not applicable □

**D.8. If Yes, When do you plan to have more children?**
_____
**D.9 Are any other household members HIV infected?** Yes □ No □
*(Ingaba bakhona abanye abantu ekhaya abosuleleke yintsholongwane kagawulayo)*
**D.10 If Yes who?[relationship to child]_____**
*(Ukuba ewe, ngubani)*
**D.11. Is anyone else, other than the child, on ARV treatment? Yes □ No □**
*(Ingaba ukho omnye umntu ngaphandle komntwana okunyango lukaGawulayo)*
**D.12. If yes, specify *Ukuba ewe,***
*chaza)*_____
[If interviewee's status mentioned, skip to 16]
**D.13. Do you know your HIV status?** Yes □ No□ [if no, go to D.18.]
*(Ingaba uyasazi isimo sakho malunga nentsholongwane kaGawulayo)*
**D.14. Are you HIV positive?** Yes □ No□ [if no, go to D.18.]
*(Ingaba unayo letsholongwane)*
**D.15. Are you on antiretroviral treatments?** Yes □ No□ [if no, go to D.18.]
*(Ingaba ukunyango lwamachiza entsholongwane kaGawulayo)*
**D.16. When did you start treatment?** (mm/yyyy) ___/_____
*(Uluqale nini olunyango)*
**D.17. Have you skipped any doses of your medication in the last 3 days?**
*(Ukhe waphosa ukusela ipilisi zakho kwezintsuku zintathu zidlulileyo)* Yes □ No□
**D.18. Do you have any chronic health problems?** Yes □ No□ [if no, go to D.20]

*(Ingaba unengxa ebalaseleyo ngokwempilo)*

**D19. If yes, specify health problems** _____

*(Ukuba ewe, chaza ingxaki)*

**D.20. Have you ever had TB**? Yes □ No□ [if no, go to D.24.]

*(Ingaba wakhe wanesifo sephepha – iTB)*

**D.21. When did you last have TB**? (mm/yyyy)_____

*(Ugqibele nini ukuba neTB)*

**D.22. Did you complete treatment?** *(Walugqiba unyango)*Yes □ No□

[if yes, go to D.24]

**D.23. What is the reason for not completing TB treatment**?

*(Yintoni eyabangela ungalugqibi unyango lwe TB)*

_____

**Child care arrangements**

*(Ulungiselelo malunga nenkathalelo yomntwana)*

**D.24.Who looks after the child during the day?**

*(Ngubani ogcina umntwana emini)*

1= attends school
*(Uhamba isikolo)*
2= attends day care centre/crèche
*(Uhamba indawo yabantwana)*
3=mother
*(Umama)*
4=grandmother
*(Umakhulu)*
5= no regular care-taking (Specify):_____
*(Akukho mntu usisigxina – chaza)*
9= Other (specify eg. Neighbour, aunt, etc) _____
*(Enye – umzekelo: umelwane, uAnti)*

**D.25.With whom does the child live (go home to at night)?** *(Uhlala nabani umntwana endlini)*

1=Both biological parents
*(Abazali bobabini)*
2=biological mother
*(Umama)*
3=biological father
*(Utata)*
4=grandmother
*(Umakhulu)*
5= Aunt
*(U-Anti)*
9= Other (specify) *(Enye – chaza)*_____

**D.26. Does the child sleep over at another caretaker for part of the week eg.** Weekends?(*Ingaba umntwana ukhe alale komnye umntu ogcinayo kwezinye intsuku zeveki: umz. Impelaveki)*

Yes□ No□

**D.27. If yes, specify** _____

*(Ukuba ewe, chaza)*

**D.28. Does your child ever sleep over with family or friends**?
*(Ingaba umntwana wakho ukhe alale kwisizalwane sakho okanye kumhlobo wakho)*
1=sometimes *(ngamanye amaxesha)* □
2= always *(ngamaxesha onke)* □
3= never *(zange)* □

**D.29. If yes, do you send the medication along with instructions how to give it**?
Yes□ No□

*(Ukuba ewe, ingaba uyanikela nangamayeza kwanemigaqo ekufuneka enikwe ngayo)*

**D.30. Does the person to whom the child goes, know his/her HIV status?**
Yes□ No□
*(Ingaba lomntu umntwana aya kuye uyazi ngesimo somntwana malunga nentsholongwane kaGawulayo)*

**E. Reasons for starting Treatment (*Izizathu zokuqalisa unyango)***

**E.1. The reason/s why I agreed to start my child on ARV is/are:**
*(Iz/sizathu esabangela ndivume ukuqalisa umntwana wam unyango luka gawulayo)*
1=the child was very sick in hospital and the doctors recommended ARVs
*(Umntwana ebegula kakhulu esibhedlele waze uGqirha wacebisa ukuba aqalise unyango)*
2= the child was always sick and the doctors recommended
*(Umntwana ebesoloko egula waze uGqirha wacebisa njalo)*
3= the child was always sick and I asked the doctors for ARVs *(Umntwana ebesoloko egula ndaze ndacela uGqirha ngamachiza onyango)*
4= the child was not sick but the doctors recommended
*(Umntwana ebengaguli waze uGqirha wacebisa)*
9= Other (specify)_____
*(Enye – chaza)*

**E.2. Is the child on any medication OTHER than ARVs?** (include prescription and home remedies) Yes □ No □
*(Ingaba lo mntwana ukunyango OLULOLUNYE ngaphandle kolu lamachiza entsholongwane kaGawulayo)* [If no, skip to F.1. ]

**E.3. If yes(specify)_____**
(Ukuba ewe – chaza)

**E.4. State purpose of other medication (include prescription medication):**
_____

**F. Disclosure, Stigma & Discrimination**
***(Ukuxelela abantu, ukungamkeleki kwakunye nokuhlekumezwa)***
***(Ukuchazela umntwana)***
**F.1. When was the child first diagnosed with HIV infection?** [Year]_____
*(Umntwana uqale nini ukwazeka ukuba wosulelekile yile ntsholongwane)*

**F.2. Have you told the child about his/her HIV status**? Yes □ No □
*(Ingaba umntwana wamxelela ngokuba uphila nale ntsholongwane)*

**F.3. What have you told the child about the reason for his/her hospital visits?**
*(Umxelele ntoni umntwana malunga nezizathu zotyelelo lwakhe apha esibedlele)*

_____

**F.4. What do you think the child knows about HIV?**
*(Ucinga ukuba umntwana wazintoni malunga nentsholongwane kaGawulayo)*

_____

**F.5. When do you think is the right time and age to talk to the child about HIV?**
*(Ucinga ukuba liliphi ixesha elilungileyo nonyaka, wokuthetha nomntwana malunga nalentsholongwane)*

_____

**F.6. Who is the best person to start this discussion with the child?**
*(Ngubani oyenamntu olungileyo wokuqalisa lencoko nomntwana)*

_____

F**.7. How do you think the clinic can assist you with telling your child?**
*(Ucinga ukuba ikliniki ingakuncedisa njani ukuxelela umntwana wakho)*

_____

_____

**F.8. Who have you told about the child's HIV status?**
*(Ngubani omxeleleyo malunga nokugula komntwana yile ntsholongwane)*

_____

**F.9. Did you receive any 'bad reactions from people you've told?** Yes □**No** □
*(Ingaba wafumana ukungamkeleki ebantwini owabaxelelayo)*

**F.10. If Yes, describe the 'bad reaction'**
*(Ukuba ewe, chaza izinto abazenzayo)*

**Describe the incident:**

_____

_____

_____

_____

**How did you respond?**

_____

_____

_____

_____

**What is it like now?**

_____

_____

_____

_____

**G. Support** ***(Inxaso)***

**G.1. Do you attend a support group regularly**? Yes□ No□ [if no, skip to G.4]
*(Ingaba uyalihamba iqela lenxaso rhoto)*

**G.2. Where do you attend a support group**?[circle appropriate number below]
*(Ulihamba phi)*
1=at the hospital *(esibhedlele)*
2= at the clinic where I live *(kwikliniki apho ndihlala khona)*
3= at the church *(ecaweni)*
4= at an NGO *(kwiqumrhu elizimeleyo)*
5= Other *(Enye)* [specify - *chaza*]_____

**G.3. What is your opinion about the support group you attend**?

_____

_____

**G.4. What do you think should be discussed or done in a support group meeting for caregivers of children on ARVs?**
1= practical tips on giving medication
2= factual information about HIV, AIDS and children
3= tips on how to start telling a child about HIV
4= stress management and coping skills
5= all of the above
6= Other, specify _____
7= did not answer
8= don't know

**G.5 The members of my household are supportive and help me.**
1= Always
2=Seldom
3= Never

**G.6. I have family living close by who are supportive and help me**. Yes No
**G.7. I have friends living close by who are supportive and help me.** Yes No

**H. ARV Administration**
***(Indlela yokuphatha lamachiza kaGawulayo)***

**H.1. Who else helps you give the child medication when you're not available to do so**?*(Ngubani ongomnye onceda ngokunika umntwana amayeza xa ungekho)*

_____

**H.2. Where is the medication stored**? *(Uwahlalisa phi amayeza)*

_____

**I would like you to describe how you fit giving medicines into your daily routine.**
(Ndizakucela undibalisele ukuba ukudibanisa njani ukunika umntwana amayeza nakwizinto ekufuneka uzenzile ngemini)

**Could you specifically describe the following:**
(Ndicela ichaze malunga noku kulandelayo)

**H.3.Explain your weekday morning routine [time you get up, and routine around giving medicines]** *(Ndicela uchaze izinto ozenza rhoqo kusasa evekini –*

**Who is responsible for the morning dose**? *Ixesha ovuka ngalo, ukuya ukunikeni amayeza)*

_____

**H3.1 What time does the child wake up**?

_____

**H3.2When do you give the child medication**? (eg. after dressing, before of after breakfast, etc)

_____

_____

**H3.3 What you use as a reminder** ?

1= cell phone alarm
2= TV programme (specify)_____
3= Other, (specify) _____
4=Routine (habit*)
9=Nothing

(* you remember when you do the same things everyday.)

**H.4. Explain your weekday evening routine**.*(Chaza izinto ezenza rhoqo ngeveki malanga)*

**H4.1 Who is responsible for the evening dose**?

_____

**H4,2 When is the child given medication** (what activity does medication administration follow?)

_____

_____

**H4.3 What do you use as a reminder tool**?

1= cell phone alarm
2= TV programme (specify)_____
3= Other, (specify) _____
4=Routine (habit)
9=Nothing

**H.5. Explain your Saturday morning routine – what happens most Saturdays?**
*(Chaza izinto ozenza rhoqo ngomgqibelo kusasa - kuqhubeka ntoni ngemigqibelo emininzi)*

**H5.1Who is responsible for giving the morning dose?** _____

**H5.2 What time does the child wake up?**_____

**H5.3 When is the medication given?** (what activity does medication administration follow?)

_____

**H5.4 What do you use as a reminder ?**

1= cellphone alarm
2= TV programme (specify)_____
3= Other, (specify) _____
4=Routine (habit)
9=Nothing

**H.6. Explain your Saturday evening routine: what happens most Saturday evenings?**
*(Chaza izinto ozenza rhoqo ngomgqibelo malanga – kuqhubeka ntoni ngemigqibelo emininzi malanga)*

_____

**H6.1 Who is responsible for giving the evening dose**_____

**H6.2 When is the medication given? (what activity does medication administration follow?)**

_____

**H6.3 What do you use as a reminder** ?

1= cellphone alarm
2= TV programme (specify)_____
3= Other, (specify) _____
4=Routine (habit)
9=Nothing

**H.7. Explain your Sunday morning routine – what happens most Sunday mornings**?

*(Chaza izinto ozenza rhoqo ngeCawe kusasa – kuqhubeka ntoni ngeCawe kusasa)*

**H7.1 Who is responsible for giving the morning dose**?_____

**H7.2 What time does the child wake up?**_____

**H7.3 When is the medication given? (what activity does medication administration follow/? _____**_____

**H7.4 What do you use as a reminder**?_____

**H.8. Explain your Sunday evening routine**.*(Chaza izinto ozenza rhoqo ngeCawe malanga)*

**H 8.1Who is responsible for giving the evening dose? _____**

**H8.2 When is the medication given? (what activity does medication administration follow?**

_____

**H8.3 What do you use as a reminder** ? _____

1= cellphone alarm
2= TV programme (specify)_____
3= Other, (specify) _____
4=Routine (habit)
9=Nothing

**H.9. When you go out, do you mostly :**

1= give the medicines before leaving home even if it is earlier than scheduled?
2= take medicines with
3= give when you return home even if it is later than scheduled
4= skip the dose if you return home too late
5= Other, specify: _____
9= did not answer

**H.10. Which of the ARVs does the child take easily [with no fuss]?**
***(Ngawaphi amachiza kula entsholongwane kaGawulayo umntwana awathatha lula –engenangxaki)***

| Drug Names | Formulation (syrup/tablet) | Ease of administration (Y/N) | Comment |
|---|---|---|---|
| 1. | | | |
| 2. | | | |
| 3. | | | |
| 4. | | | |

**H.11. What do you do when the child does not want to take the ARVs?**
***[Note to Interviewer:*** *Prompt for techniques to make medicine palatable or 'luxury bribes, coat mouth with peanut butter' etc.]*
*(Wenza ntoni xa umntwana engafuni ukuthabatha/ ukusela lamachiza)*

_____

_____

**I. Knowledge, Attitude and Practice regarding Treatment**

**I.1 Answer the following questions by choosing one of the following responses: (Phendula lemibuzo ilandelayo ngokuthi ekhethe impendulo ezilandelayo)**

| | 1=Always<br>2=Sometimes<br>3=Never |
|---|---|
| I.1 I think it is (always/sometimes/never) good to give my child a break from ARV treatment<br>*(Ndicinga ingaluncedo ukuba ndinike umntwana wam ikhefu ekuthabatheni olunyango lwalamachiza)* | |
| I.2. I (always/sometimes/never) take my child to a traditional healer<br>*(Ndiyamsa umntwana wam nako Siyazi)* | |
| I.3. I (always/sometimes/never) give all the medicines exactly at the same time each day (Monday to Sunday)<br>*(Ndiyamnika amayeza ngexesha elifanayo qho ngemini - umvulo ukuya ngolwesihlanu)* | |

**I.2 State whether you agree or disagree with the following statements?**
**(Chaza ukuba uyavumelana okanye awuvumelani noku kulandelayo)**

| | Agree | Disagree | Don't Know | If Disagree, Comment |
|---|---|---|---|---|
| I.4. Each ARV medicine/tablet I give my child works in the same way therefore I do not have to give all at the same time it is okay to leave out one sometimes. *(Iyeza/ Ipilisi nganye endiyinika umntwana isebenza ngendlela enye ngako oko akufanelekanga ukuba ndimnike rhoqo, kulungile ukushiya noba inye nagmanye amaxeshe)* | | | | |
| I.5. I know all the names and doses of the ARVs prescribed to my child [name and dosing] (Ndiyawazi onke amagama kwakunye namachiza abekelwe umntwana wam – amagama nendlela yokunika)<br>1._____<br>2._____<br>3._____<br>4._____ | | | | |
| I.6.Once the child starts getting better one can stop the treatment *(Xa umntwana eqalisa ukubangcno angaluyeka olunyango)* | | | | |
| I.7.After a while of taking the treatment the child can be cured of HIV *(Emva kwethuba umntwana ekolunyango uyaphila kule ntshalongwane iphela)* | | | | |
| I..8. My child has experienced no side-effects to the medication thus far *(Umntwana wam zange afumane ziphumo zosecaleni ukuzokuthi gha ngoku)* | | | | |
| I.9. My child will have to take this medicine for the rest of his/her life *(Umntwana wam kufuneka ethathe lamayeza ubomi bakhe bonke)* | | | | |
| I.10. I am worried about whether my child will grow up to complete school. *(Andikho sexhaleni malunga nokuba umntwana wam uzakukhula agqibe isikolo)* | | | | |
| I.11. I believe the benefits of taking the ARVs far outweigh the risks | | | | |

**Note to Interviewer: Do Not Prompt for answers below!**

**I.3. What do you think will happen if you miss 1 dose in a week?**

1= Nothing
2= Child will get sick
3= Medicine will stop working
4= the viral load will go up
5= Other (specify)_____
9= don't know

**I.4. What do you think will happen if you miss more than 3 doses in a week?**

1= Nothing
2= Child will get sick
3= Medicine will stop working
4= the viral load will go up
5= Other (specify)_____
9= don't know

**General Comments**:
Thank you for giving your time to complete this questionnaire, before you leave, is there anything else you would like to comment on regarding the child's treatment or the clinic?

## Appendix 11: Caregiver depression screening (CES_D)

| | |
|---|---|
| Enrolment No:_____ | Date of Interview:_____ |
| Interviewer: _____ | Score: /___/ |
| Study Visit No: _____(B ; 2wk; 1,3,6mth) | |

This questionnaire lists feelings and behaviour that you may have experienced during the past week. Please tell me how often you have felt this way during this past week. *(Le mibuzo icalucalula indlela oziva ngayo, nendlela zokuziphatha onokuthi kanti uthe wazifumana kwiveki egqithileyo. Nceda undixelele ukuba uzive ngoluhlobo kangakanani kwiveki egqithileyo)*

**Circle on number on each line:**

**1= Rarely or none of the time (less than 1 day)**
**(kunqabile okanye tu kweli xesha)**
**2= Some or a little of the time (1-2 days)**
**(Ngamanye or ixesha elincinci)**
**3= Occasionally or a moderate amount of time (3-4 days)**
**(Ngamaxesha athile okanye ixeshana nje)**
**4= Most or all of the time (5-7 days)**
**(Amaxesha amaninzi okanye ixesha lonke)**

**During the past week:**

| | | | | |
|---|---|---|---|---|
| 1. I was bothered by things that usually don't bother me. *(Bendikhathazwa zizinto ebezingadli ukundikhathaza)* | 1 | 2 | 3 | 4 |
| 2. I did not feel like eating; my appetite was poor. *(Akhange ndibenamdla wokutya: umdla wam ebemncinci)* | 1 | 2 | 3 | 4 |
| 3. I felt that I could not shake off the blues even with help from my family or friends. *(Ndizive ingathi andinakuvele nje ndiyeke ukutyhafa nokuba ndincedwa zizizalwane okanye abahlobo)* | 1 | 2 | 3 | 4 |
| 4. I felt that I was just as good as other people. *(Ndizive ukuba ndilungile njengabanye abantu)* | 1 | 2 | 3 | 4 |
| 5. I had trouble keeping my mind on what I was doing. *(Bendinengxaki yokubeka ingqondo yam kwinto endiyenzayo)* | 1 | 2 | 3 | 4 |
| 6. I felt depressed. *(Bendiziva ndidakumbile)* | 1 | 2 | 3 | 4 |
| 7. I felt that everything I did was an effort. *(Bendiziva okokuba yonke into endiyenzayo ibazinzame)* | 1 | 2 | 3 | 4 |
| 8. I felt hopeful about the future. *(Ndiziva ndinethemba malunga nekamva)* | 1 | 2 | 3 | 4 |
| 9. I thought my life had been a failure *(Bendicinga ukuba ubomi bam abuphumelelanga)* | 1 | 2 | 3 | 4 |
| 10. I felt fearful. *(Ndizive ndisoyika)* | 1 | 2 | 3 | 4 |
| 11. My sleep was restless. *(Bendiphuthelwa – kungekho kuphumla ebusuku)* | 1 | 2 | 3 | 4 |
| 12. I was happy. *(Ndando nwabile)* | 1 | 2 | 3 | 4 |

| | | | | |
|---|---|---|---|---|
| 13. I talked less than usual.<br>*(Ndithetha kancinci kunesiqhelo)* | 1 | 2 | 3 | 4 |
| 14. I felt lonely.<br>*(Ndinomva ndedwa)* | 1 | 2 | 3 | 4 |
| 15. People were unfriendly.<br>*(Abantu bebenganabuhlobo)* | 1 | 2 | 3 | 4 |
| 16. I enjoyed life.<br>*(Ndibuvuyele ubomi bam)* | 1 | 2 | 3 | 4 |
| 17. I had crying spells.<br>*(Bendisuka nje ndikhale)* | 1 | 2 | 3 | 4 |
| 18. I felt sad.<br>*(Bendiziva ndilusizi)* | 1 | 2 | 3 | 4 |
| 19. I felt that people dislike me.<br>*(Bendiziva ingathi abantu abandifuni)* | 1 | 2 | 3 | 4 |
| 20. I could not get "going".<br>*(Bendiziva umzimba wam uphantsi- ndingakwazi nokuqalisa na nto)* | 1 | 2 | 3 | 4 |

**Notes:**

_____
_____
_____

CES-D Score: _____

## Appendix 12: MOS Social Support Survey

| | |
|---|---|
| Enrolment No:_____ | Date of Interview:_____ |
| Interviewer: _____ | Score: /___/ |
| Study Visit: _____ | |

We would like to ask you some questions about the practical and emotional support that is available to you.
(Singathanda ukubuza imibuzo malunga nokwenzekayo kwakunye nenxaso yokuzwelana nawe )othi uyifumane)

1. About how many close friends and close relatives do you have (people you feel at ease with and can talk to about what is on your mind)?
(Malunga nokuba bangaphi abahlobo kwkunye nezizalwane ezisondeleleyo onazo)
[Abantu ochinga ukuba balulutho kwaye unagthetha nabo malunga nokucingayo]

Write in number of close friends and close relatives
(Bhala inani labahlobo abasondeleleyo kwakunye nezizalwane ezisondeleyo)

People sometimes look to others for companionship, assistance or other types of support. I will ask you about specific situations and you will tell me how often each of the various kinds of support is available to you if you need it and whether or not you are satisfied with the different kinds of support you receive. [You may use the scale in front of you.]

(Abantu ngamanye amaxesha bajonga abanye abantu njengabangane, abancedi, okanye njengolunye uhlobo lwenxaso. Ndizakubuza malunga nemeko ezithile uze undixelele ukuba lixesha elingakanani kulamancedo akhankanyiweyo othi ulifumane xa ulifuna nokuba uyaneliseka okanye hayi ngalamancedo ahlukeneyo othi uwafumane)

**Note to Interviewer: Circle one number on each line**

**1= None of the time [Akukho nalinye ixesha]**
**2=A little of the time [Ixesha elincinci]**
**3=Some of the time [Amaxesha athile]**
**4=Most of the time [Amaxesha amaninzi]**
**5=All of the time [Amaxesha onke]**

| | | | | | | |
|---|---|---|---|---|---|---|
| 1. Someone to help you if you were confined to bed<br>*(Umntu wokunceda ukuba ngaba ububambekile ebhedini)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 2. Someone you can count on to listen to you when you need to talk.<br>*(Umntu onokuxhomekeka kuye onokumamela kuwe xa ufuna ukuthetha)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 3. Someone to give you good advice about a crisis.<br>*(Umntu onokunika ingcebiso ezintle malunga nengxaki)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 4. Someone to take you to the doctor if you needed it.<br>*(Umntu onokuthi akuse kwagqirha ukuba ngaba uyafuna)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 5. Someone who shows you love and affection.<br>*(Umntu obonakalisa uthando nenkathalelo)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 6. Someone to have a good time with.<br>*(Umntu othi ubenexesha elimnandi naye)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 7. Someone to give you information to help you understand a situation.<br>*(Umntu onokunika izimvo zokuzinceda ukuba uqonde malunga nemeko ethile)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 8. Someone to confide in or talk to about yourself or your problems.<br>*(Umntu onokuthi umhlebele okanye nincokole malunaga nawe kunye nengxaki yakho)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 9. Someone who hugs you.<br>*(Umntu okuwongayo)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 10. Someone to get together with for relaxation.<br>*(Umntu ohlala naye xa upholile)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 11. Someone to prepare your meals if you were unable to do it yourself.<br>*(Umntu okwaziyo ukulungiselela isidlo xa wena ungakwazi ukwenza njalo)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 12. Someone whose advice you really want.<br>*(Umntu ofuna ezona ingcebiso zakhe)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 13. Someone to do things with to help you get your mind off things.<br>*(Umntu owenza izinto naye ukunceda ingcinga zakho okokuba zisuke ezintweni)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 14. Someone to help with daily chores if you were sick.<br>*(Umntu okunceda malunga nezinto zangemihla ukuba ubugula)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 15. Someone to share your most private worries and fears with.<br>*(Umntu owabelana naye nemfihlelo zakho kwakunye noloyiko)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 16. Someone to turn to for suggestions about how to deal with a personal problem.<br>*(Umntu onokubhenela kuye ngengcebiso malunga nokusombulula ingxaki yakho)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 17. Someone to do something enjoyable with.<br>*(Umntu uwenza into eyonwabisayo naye)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 18. Someone who understands your problems.<br>*(Umntu oyiqondayo ingxaki yakho)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 19. Someone to love and make you feel wanted.<br>*(Umntu okuthandayo nokwenza uzive usafuneka)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |
| 20. Someone to help take care of your children when you can't.<br>*(Umntu onokunceda ukukhathaleleni abantwana xa ungakwazi)* | 1 | 2 | 3 | 4 | 5 | ☺…☹ |

# Appendix 13: Caregiver self-report questionnaire

06-21-04 10:22 AM (gr) DRAFT

QLW0076(P1041)/06-08-04

## PEDIATRIC INTERNATIONAL ADHERENCE QUESTIONNAIRE

Behavior/Identification

NIAID PEDIATRIC AIDS CLINICAL TRIALS GROUP



Patient Number ☐☐☐ ☐☐☐☐☐ Date of Patient Visit/Contact ☐☐☐ mmm ☐☐ dd ☐☐☐☐ yyyy

Protocol Number P 1 0 4 1 ☐ Institution Code ☐☐☐☐☐☐

Form Week ☐☐☐ * Seq. No. ☐ ** Step No. ☐☐ Key Operator Code ☐☐☐

* Enter a "1" if this is the first of this form for this date. Designate subsequent forms on same date with a 2, 3, etc.
**Enter the subject's current study step number. Enter '1' if the study does not have multiple steps.

FOR OFFICE USE ONLY - TEAR OFF SHEET

The **purpose** of this questionnaire is to collect data which will quantify the proportion of prescribed INH/placebo therapy actually taken within the last 3 days in order to examine drug effect during the analysis phase of a study protocol. In order to have confidence in the data that will be collected with this instrument, the **process** through which these data are collected has been **standardized**.
Please read and observe the following directions.

**Who administers?** Any member of the professional clinical care or research team who has experience filling out other ACTG study forms.

**Who is questioned?** The study participant, if the study participant has assumed responsibility for his/her own drug regimen OR the study participant's primary caregiver (the person responsible for administering the prescribed drugs at home). If the appropriate respondent is the primary caregiver and she/he is not present for a particular study visit when this form is scheduled, the form should be marked as such (below) and the assessment omitted.

**How is the questionnaire administered?** The questionnaire has very specific introductory comments (and prompts) which should be read as stated, item after item, until the assessment is completed. No interruptions for study participant education should occur; any necessary or additional education or counseling should take place after the questionnaire is completed.

The accuracy of self report is very good if the attitude of the interviewer is non-judgmental and supportive. The form has introductory statements to set this tone. However, since information about erratic adherence may be elicited by the survey, what interaction happens after the questionnaire is completed is critically important. The attitude of the clinical response, the manner in which information is subsequently corrected, and the nature of behavioral counseling will **absolutely** influence future validity. It is imperative that clinical teams review the characteristics of therapeutic relationships and strive to adopt these practices in promoting drug adherence in study participants.

**QUESTIONS 1 - 3 ARE TO BE COMPLETED BY THE STUDY NURSE:**

1. Was the questionnaire completed at this visit? ..... (1-Yes, 2-No) ☐
   If Yes, go to question 2.
   If No, complete 'a' and STOP.
   a. Indicate the reason the questionnaire was not completed: .... ☐☐
      11-Study participant refused
      12-Primary caregiver refused
      13-Study participant missed clinic visit
      14-There was not enough time
      15-Primary caregiver not available
      99-Other reason, specify
      If Other, specify [30]: _____

2. Who responded to the questions? ☐☐
   11-Study participant
   12-Biological mother
   13-Biological father
   14-Grandmother
   15-Grandfather
   16-Foster mother
   17-Foster father
   18-Stepmother
   19-Stepfather
   99-Other, specify
   If Other, specify [30]: _____

3. Who is responsible for administering the medications? ☐☐
   11-Primary caregiver solely responsible
   12-Study participant solely responsible
   13-Study participant and caregiver jointly
   14-Study participant and other individual
   99-Other, specify
   If Other, specify [30]: _____

06-08-04

QLW0076(P1041)/06-08-04

## PEDIATRIC INTERNATIONAL ADHERENCE QUESTIONNAIRE



Pt. No. ☐☐☐☐☐☐☐ * Seq. No. ☐ ** Step No. ☐☐ Date ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

**INSTRUCTIONS FOR COMPLETION OF MEDICATION TABLE**

- **Columns A-D:** Prior to the study visit, the study nurse should fill in the information in these columns for **which adherence information is being collected as specified by the protocol.**
- **Column A:** List the drug name (if known or, if double-blinded study, record as marked on bottle).
- **Column B:** List the eight digit drug code for the drug listed in Column A. Refer to Appendix 3 or by using the Drug Code Lookup Program at the DMC Web Site (www.fstrf.org).
- **Column C:** List the drug color, type (blue pill, pink liquid, etc.) and note any special identifying labels.
- **Column D:** List the expected number of **doses** per 24 hour period. This refers to the **schedule** (e.g. 3 times per day, 4 times per day) and **not** the number of pills. Particulars of the schedule will not be addressed (e.g. TID and q8 hr. would both be recorded as 3 times per day).
- **Columns E-I:** This information is to be obtained from the study participant or primary caregiver in the subsequent interview. Refer to "Scripts for Pediatric Adherence Questionnaire Module 1 – Revised" for completing the Medication Table. This document is located in the Forms Instruction section of the CRF Notebook.
- **Column J:** Indicate if there were any problems or situations since the last visit that made it hard to take/give your baby/child this medication every day.

4. MEDICATION LIST TABLE: **Do not key Column C.**

[1] Identification Codes
1-Volunteered without prompt
2-Volunteered with prompt
3-Acknowledged when reminded
4-Did not acknowledge

[2] Doses Missed
Enter "-1" if study participant isn't sure if he/she missed any doses.
Enter "0" if no doses were missed.

| Complete Prior to Visit | | | | Complete During Interview | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| A | B | C | D | E | F | G | H | I | J |
| | | | | | | Doses Missed [2] | | | |
| Drug Name(s) [30]: | Drug Code [8]: | Drug Color, Type and Labels | Expected # Doses | ID Code[1] | Reported # Doses | Yesterday | 2 days ago | 3 days ago | Any Problems? (1-Yes, 2-No) |
| a. | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. | | | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

5. When was the last time your baby/child missed a dose of any of these medications?..... ☐

1-Never
2-During the previous 2 weeks
3-During the last month
4-Over a month ago
5-Don't remember

QLW0076(P1041)/06-08-04

## PEDIATRIC INTERNATIONAL ADHERENCE QUESTIONNAIRE



Pt. No. ☐☐☐☐☐☐☐ * Seq. No. ☐ ** Step No. ☐☐ Date ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

**INSTRUCTIONS FOR COMPLETION OF DRUG SPECIFIC TABLE:**

Enter the drug code of each medication that the study participant was non-adherent to or identified as having a problem taking.

**Identification of Reasons for Non-Adherence:**

*READ the following paragraph to the study participant or primary caregiver:*

"Many people at one time or another have trouble with these medications. We would like to better understand the things that make giving medications hard for families. These are some of the reasons others have identified which have made it difficult to take [give] all of the medications."

*Show and read the list of reasons to the study participant or primary caregiver.*

*After the list is read, ask the following question for each drug:*

"Have any of the following been problems for you with _____(drug name or characteristics)_____?"

*If "Yes," enter the frequency code for each reason.*
*If "No," go to the next drug.*
*For data entry, use the tab key after the last entry on the page.*

**DRUG SPECIFIC ADHERENCE DIFFICULTIES:**

Frequency Codes

*Use these codes to indicate how often the listed reason makes it harder to take (give) each of the medications the study participant is taking.*

0-Never
1-(1-2) times per month
2-(1-2) times per week
3-(≥ 3) times per week

| | *Drug #1 Code* [8]: _____ | *Drug #2 Code* [8]: _____ | *Drug #3 Code* [8]: _____ | *Drug #4 Code* [8]: _____ | *Drug #5 Code* [8]: _____ |
|---|---|---|---|---|---|
| 6. Reasons for Non-adherence: | | | | | |
| a. I ran out of medicine; didn't come for medicine ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. The medicine tastes bad ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. I just forgot ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. I was worried about the side effects .... | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. There was a change in daily routine ... | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. Too busy with the baby/child ..... | ☐ | ☐ | ☐ | ☐ | ☐ |

QLW0076(P1041)/06-08-04

# PEDIATRIC INTERNATIONAL ADHERENCE QUESTIONNAIRE



Pt. No. ☐☐☐☐☐☐☐ * Seq. No. ☐ ** Step No. ☐☐ Date ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

**INSTRUCTIONS FOR COMPLETION OF DRUG SPECIFIC TABLE:**
Enter the drug code of each medication that the study participant was non-adherent to or identified as having a problem taking.

**Identification of Reasons for Non-Adherence:**

***READ the following paragraph to the study participant or primary caregiver:***
"Many people at one time or another have trouble with these medications. We would like to better understand the things that make giving medications hard for families. These are some of the reasons others have identified which have made it difficult to take [give] all of the medications."

***Show and read the list of reasons to the study participant or primary caregiver.***

***After the list is read, ask the following question for each drug:***
"Have any of the following been problems for you with _____(drug name or characteristics)_____?"

***If "Yes," enter the frequency code for each reason.***
***If "No," go to the next drug.***
***For data entry, use the tab key after the last entry on the page.***

**DRUG SPECIFIC ADHERENCE DIFFICULTIES:**

Frequency Codes
*Use these codes to indicate how often the listed reason makes it harder to take (give) each of the medications the study participant is taking.*
0-Never
1-(1-2) times per month
2-(1-2) times per week
3-(≥ 3) times per week

| | *Drug #1 Code* [8]: _____ | *Drug #2 Code* [8]: _____ | *Drug #3 Code* [8]: _____ | *Drug #4 Code* [8]: _____ | *Drug #5 Code* [8]: _____ |
|---|---|---|---|---|---|
| 6. **Reasons for Non-adherence:** | | | | | |
| a. I ran out of medicine; didn't come for medicine …….. | ☐ | ☐ | ☐ | ☐ | ☐ |
| b. The medicine tastes bad …….. | ☐ | ☐ | ☐ | ☐ | ☐ |
| c. I just forgot ……..…. | ☐ | ☐ | ☐ | ☐ | ☐ |
| d. I was worried about the side effects …. | ☐ | ☐ | ☐ | ☐ | ☐ |
| e. There was a change in daily routine … | ☐ | ☐ | ☐ | ☐ | ☐ |
| f. Too busy with the baby/child …… | ☐ | ☐ | ☐ | ☐ | ☐ |

## PEDIATRIC INTERNATIONAL ADHERENCE QUESTIONNAIRE



Pt. No. ☐☐☐☐☐☐☐ * Seq. No. ☐ ** Step No. ☐☐ Date ☐☐☐ (mmm) ☐☐ (dd) ☐☐☐☐ (yyyy)

**Frequency Codes**

*Use these codes to indicate how often the listed reason makes it harder to take (give) each of the medications the study participant is taking.*

0-Never
1-(1-2) times per month
2-(1-2) times per week
3-(≥ 3) times per week

| | *Drug #1 Code* [8]: _____ | *Drug #2 Code* [8]: _____ | *Drug #3 Code* [8]: _____ | *Drug #4 Code* [8]: _____ | *Drug #5 Code* [8]: _____ |
|---|---|---|---|---|---|
| 6. **Reasons for Non-adherence:** | | | | | |
| q. My baby/child was well ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| r. There was too much medicine to give | ☐ | ☐ | ☐ | ☐ | ☐ |
| s. I was away from home ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| t. I was busy with other things ..... | ☐ | ☐ | ☐ | ☐ | ☐ |
| u. Other, specify ..... [30]: _____ | ☐ | ☐ | ☐ | ☐ | ☐ |

*For Protocol P1041:*

Country: Enter 'SA' in the country box for South Africa.

Language: Enter 'E' if the scripts were read to the study participant in English.
Enter 'A' if the scripts were read to the study participant in Afrikaans.
Enter 'X' if the scripts were read to the study participant in Xhosa.
Enter 'Z' if the scripts were read to the study participant in Zulu.
Enter 'So' if the scripts were read to the study participant in Sotho.

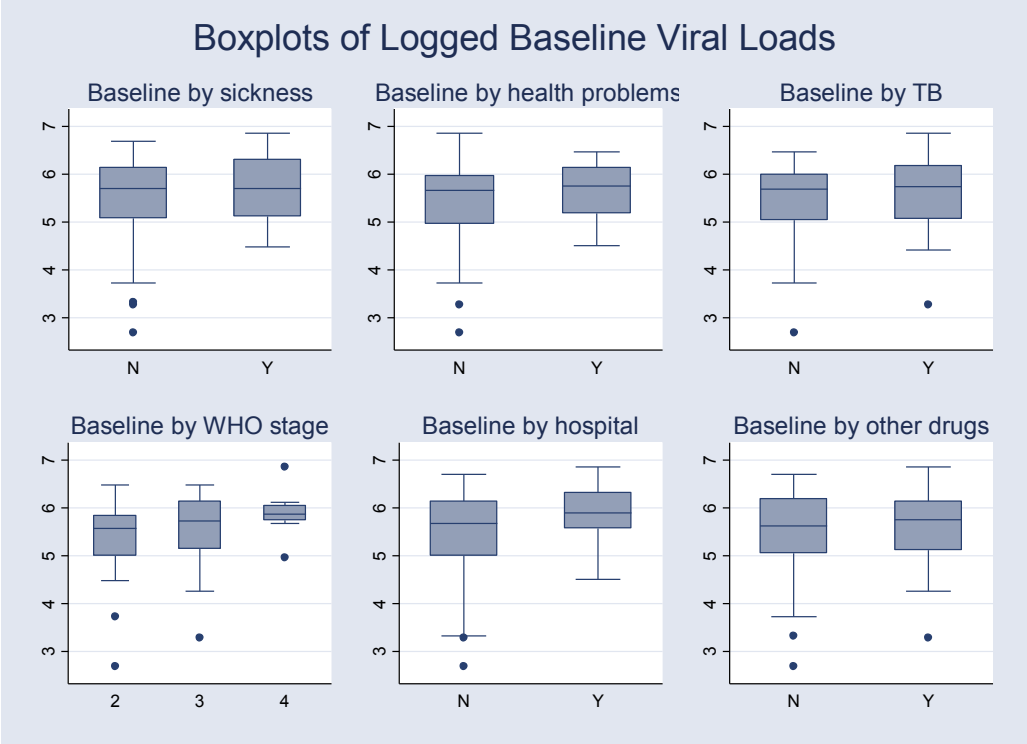
Country: ☐☐ Language: ☐☐



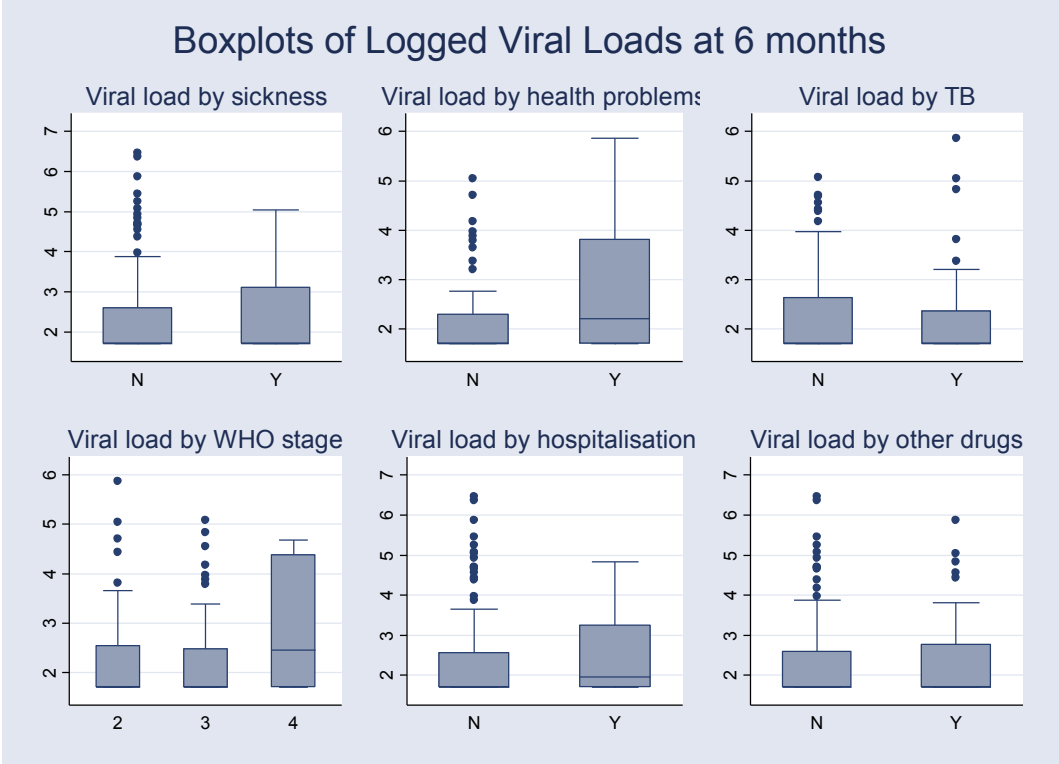
Date Form Keyed (DO NOT KEY): _____ / _____ / _____

# Appendix 14: Boxplots

**Correlation between potential confounders and Baseline Viral load**




**Association between potential confounders and 6 month viral load**



# Appendix 15: Regression Models correlates of adherence

## Backwards Stepwise regression analysis with (pr 0.1)

Variables entered into model:

sw logistic adherence agemo recentsick dayslasthosp Otherdrugs since housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender Health Prob IDattend CurrentTB, pr(0.1)

**23 variables**

**N= 119**

| adherence | Odds Ratio | Std. Err. | z | P>\|z\| | [95% CI] | |
|---|---|---|---|---|---|---|
| PMTCT | 0.35 | 0.20 | -1.81 | 0.07 | 0.12 | 1.09 |
| since | 0.99 | 0.00 | -2.30 | 0.02 | 0.10 | 1.00 |
| dayslasthosp | 1.00 | 0.00 | 1.65 | 0.10 | 1.00 | 1.00 |
| Counsel | 3.71 | 2.09 | 2.34 | 0.01 | 1.24 | 11.17 |

Variables entered into model:

sw logistic adherence agemo recentsick dayslasthosp Otherdrugs since housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender Health Prob IDattend CurrentTB, pr(0.1)

| 25 variables | | | | | | |
|---|---|---|---|---|---|---|
| N=86 | | | | | | |
| adherence | OR | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
| Grants | 4.89 | 3.77 | 2.06 | 0.03 | 1.08 | 22.11 |
| recentsick | 18.54 | 21.38 | 2.53 | 0.01 | 1.93 | 177.82 |
| Planmore | 0.20 | 0.18 | -1.82 | 0.069 | 0.03 | 1.13 |
| Counsel | 6.24 | 5.46 | 2.09 | 0.036 | 1.12 | 34.66 |
| since | 1.00 | 0.00 | -2.32 | 0.020 | 1.00 | 1.00 |
| HealthProb | 0.11 | 0.10 | -2.47 | 0.013 | 0.02 | 0.64 |
| IDattend | 59.34 | 77.34 | 3.13 | 0.002 | 4.61 | 763.53 |
| CurrentTB | 0.09 | 0.08 | -2.54 | 0.011 | 0.013 | 0.57 |
| Housing | 0.12 | 0.11 | -2.29 | 0.022 | 0.02 | 0.73 |
| depressd | 0.03 | 0.05 | -2.14 | 0.032 | 0.00 | 0.74 |

**27 variables**

**N=86**

Variables entered into model

sw logistic adherence agemo recentsick monthlasthosp Otherdrugs IDduration housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender HealthProb IDattend CurrentTB Grants dep9 fldwh~hz fldw~waz fldw~haz, pr (0.1)* excluding SigLE

| adherence \| | OR | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| CurrentTB \| | 0.16 | 0.13 | -2.31 | 0.02 | 0.03 | 0.76 |
| recentsick \| | 4.34 | 3.58 | 1.78 | 0.08 | 0.86 | 21.87 |
| IDattend \| | 14.74 | 14.51 | 2.73 | 0.01 | 2.14 | 101.47 |
| HealthProb \| | 0.23 | 0.17 | -2.00 | 0.05 | 0.06 | 0.97 |
| IDduration \| | 0.97 | 0.02 | -1.78 | 0.08 | 0.93 | 1.00 |
| PMTCT \| | 0.20 | 0.13 | -2.38 | 0.02 | 0.05 | 0.75 |
| Grants \| | 5.15 | 3.50 | 2.41 | 0.02 | 1.36 | 19.49 |

29 VARIABLES

N=56

Variables entered into model

. sw logistic adherence agemo recentsick monthlasthosp Otherdrugs IDduration housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender HealthProb IDattend CurrentTB Grants dep9 fldwh~hz fldw~waz fldw~haz LE maritalstatus, pr (0.1)

| adherence \| | OR | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| CurrentTB \| | 0.22 | 0.17 | -1.97 | 0.05 | 0.05 | 1.00 |
| PMTCT \| | 0.15 | 0.12 | -2.30 | 0.02 | 0.03 | 0.75 |
| IDduration \| | 0.96 | 0.02 | -1.88 | 0.06 | 0.92 | 1.00 |
| housedensity \| | 1.38 | 0.23 | 1.97 | 0.05 | 1.00 | 1.90 |

22 VARIABLES

N=119

Variables entered into model

sw logistic adherence agemo recentsick monthlasthosp Otherdrugs IDduration housedensity Stage Reltochild PMTCT GiverAge Educ Employment Planmore Anyother Counsel Access PostSchool Housing Gender HealthProb IDattend CurrentTB, pr(0.1)

(Excluding depression, sigle, fldwh~hz fldw~waz fldw~haz 'maritalstatus and grants)

| adherence | OR | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| PMTCT | 0.36 | 0.20 | -1.81 | 0.07 | 0.12 | 1.09 |
| IDduration | 0.95 | 0.02 | -2.30 | 0.02 | 0.91 | 1.00 |
| monthlasth~p | 1.06 | 0.04 | 1.65 | 0.10 | 0.99 | 1.13 |
| Counsel | 3.71 | 2.09 | 2.34 | 0.02 | 1.24 | 11.17 |