Assessing reported adherence to antiretroviral therapy using the method of verbal recall in children from Kwa-Zulu Natal, South Africa

By

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As the candidate's supervisor I have/have not approved this thesis for submission.

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I.......................Dr Hassina Ebrahim...declare that

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Acknowledgements

Overview

Sub-Saharan Africa has the highest number of children living with HIV. HIV is one of the major causes of under-five mortality in Africa. Antiretroviral therapy in the paediatric population has improved mortality, led to a better quality of life, as well as overall health and well-being of children. Adherence is a critical factor in determining treatment outcomes and success. Non-adherence to therapy increases risk of treatment failure, delays immunological recovery and increases opportunistic infections.

In the paediatric population, there is a paucity of studies assessing adherence rates, particularly in resource limited settings. Adherence behaviour is found to be more complex in children. A number of factors affect adherence in children. These include socio-economic factors, medication factors as well as healthcare provider dynamics.

The purpose of this secondary analysis of a prospective study was to describe adherence in a cohort of children attending a regional hospital in Kwa-Zulu Natal, South Africa, from September 2006 until October 2009. This study also examined factors associated with adherence such as age of the child, gender, as well as the role of the primary caregiver. Since there is no "gold standard" for assessing adherence to antiretroviral therapy, this area of research needs to be explored further. Secondly, assessing factors associated with adherence will assist in looking at ways to improve treatment outcome.

In the main study, prospective patients who were treatment naïve and met criteria to commence antiretroviral therapy were identified in outpatients and clinics. Baseline

and follow-up questionnaires were used to capture information including adherence details over the preceding week as well as since the last visit to hospital. Adherence was assessed using the method of verbal recall. Missed doses and the reasons for these were recorded and analysed. Additional factors possibly associated with adherence were also recorded and analysed further.

This study reported an overall adherence rate of 94 per cent, similar to rates reported in other studies. Adherence rates over the past week as well as since the patient's last visit were similar. There was a substantial degree of agreement between verbal recall for the preceding week as well as since the last visit (kappa statistic 0.64, p < 0.005). It was found that children older than five years were more likely to be adherent than those under five years (OR 0.871, 95 % CI 0.22-3.376) and males were twice as likely to adhere as females (OR=2.05, 95% CI 0.49 -8.59).

The impact of this study is that it will provide information on adherence in children in Kwa-Zulu Natal, South Africa. This could encourage other such studies to be undertaken to improve adherence rates and hence treatment success. By examining factors associated with adherence as well as identifying possible barriers, we may improve treatment success in children.

Adherence to antiretroviral therapy is important, especially in the paediatric population as it is shown to increase survival, improve immunity, as well as help prevent the development of opportunistic infections. Sub-optimal adherence is associated with treatment failure and drug resistance. The use of verbal recall as a measure of adherence is useful in a resource limited setting.

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Chapter 1:

Literature review

According to UNICEF, there were 36.9 million people globally living with HIV at the end of 2014. Sub-Saharan Africa bears 91% of the global burden of the disease. HIV and AIDS estimates for 2014 revealed that there were 6 800 000 people living with the disease in South Africa. The number of children between the ages of 0 – 14 was 340 000 [1]. As of June 2015, there were 15.8 million people accessing antiretroviral (ARV) therapy. There has been a 58% decrease in new HIV infections among children since 2000. Worldwide, approximately 220 000 children became newly infected with HIV in 2014 [2].

The majority of children are infected with HIV via mother-to-child transmission either during pregnancy, labour or breastfeeding. In 2002, a Prevention of Mother-to-Child Transmission programme (PMTCT) began in South Africa. In 2010, the Department of Health revised the PMTCT policy to include daily nevirapine for six weeks for all infants born to HIV-Positive women and to be continued for breastfeeding mothers who were not on ART to reduce post-natal transmission [3]. Accordingly, the mother-to-child transmission rates decreased to 2.7% in 2011 [3].

 The National Consolidated Guidelines for the prevention of mother-to-child transmission of HIV and the management of HIV-infected children, adolescents and adults in 2015 recommended birth PCR HIV testing of all HIV-exposed neonates, to be repeated at ten weeks and rapid HIV testing at eighteen months. For those on

extended twelve-week nevirapine, the PCR is to be repeated at eighteen weeks and a rapid HIV test at eighteen months. The goal is to initiate treatment early and allow for more opportunities to test both mother and child.

There has been a significant upscaling of the ART programme in South Africa. On 1 April 2004, ART initiation began at several service points across the country. By March 2005, all provinces had begun initiating ART. From then on, there have been advances in care and delivery to all HIV-infected patients. In 2010, the South African Department of Health revised its ARV guidelines, expanding treatment to all children under one year of age, all pregnant women regardless of CD4+ count and all TB-HIV co-infected patients with a CD4+ count of <350. Only 55% of adults and 36% of children eligible for ART were receiving it by the end of 2010 [4]. In 2012, a decision was made to expand access thresholds for children [4].

ART suppresses HIV replication, prevents opportunistic infection, improves well-being of children and adults and increases life expectancy. Hence, assessing the level of adherence is important as non-adherence will affect treatment outcomes. Despite this, the UNAIDS Gap Report 2014 revealed that 62% of children living with HIV have not accessed treatment [5].

In the Children with HIV Early Antiretroviral (CHER) trial, early ART was compared with a deferred approach in infants <12 weeks of age and with a baseline CD4 count of more than 25%. Infants entered the trial at a median of seven weeks of age [6]. Children on early therapy had a significant reduction in mortality and disease progression. There was also an improvement in developmental outcomes. In an

earlier multi-cohort study in 2008, of seven public sector paediatric ART programmes in Gauteng, Western Cape and KwaZulu-Natal provinces, outcomes of the South African National Antiretroviral Treatment programme for children were looked at. Dramatic clinical benefit was seen, with suppression of viral load and a low mortality rate of 7.7% in a large cohort of 6078 children. These studies demonstrate the success of ART in children as well as significant reductions in morbidity and mortality [7].

In a study by Meyers et al., examining ART responses in children attending a large public clinic in Soweto, South Africa, it was found that 84% – 96% of children achieved virological suppression by 12 – 24 months [8]. Furthermore, after ART initiation, immunological improvement was demonstrated by the mean CD4% having doubled within twelve months, rising from 12.7% (95% CI: 11.9%, 13.4%) at baseline, to 25.1% (95% CI: 24.4%, 25.8%). Growth parameters were also found to have improved after initiation of ART [8]. In another South African study in KwaZulu-Natal by Reddi et al., outcomes of ART in 151 patients were scrutinised. Similarly, these patients had an improvement in clinical and immunological parameters on commencement of ART. There was an increase in the cohort's CD4% from baseline at six months (p <0.001). Viral load for 100 children at six months revealed 84% (95%CI 80.3–87.7) had undetectable levels. In all, 65 out of a total of 88 children (73.8%) had a significant increase (P < 0.001) in weight for age Z-score after the first month of treatment [9].

The World Health Organisation (WHO) defines adherence as the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider

[10]. Adherence and compliance have been used interchangeably in clinical practice and essentially refers to patients' efforts to follow healthcare advice. HIV is a chronic condition for which therapy is for a lifetime. Adherence also encompasses health-related behaviours that extend beyond taking prescribed medication. Seeking medical help, taking medication appropriately and timeously, attending follow-up appointments, and executing behavioural modifications are all examples of therapeutic behaviour patterns. At the US Centres of Disease and Control (CDCs) Noon Conference in 2013, medication adherence was defined as: "The patient's conformance with the provider's recommendation with respect to timing, dosage, and frequency of medication-taking during the prescribed length of time."

Adherence may be measured using either process-oriented or outcome-oriented definitions. Outcome-orientated definitions use the end-result of treatment, e.g., cure rate, as an indicator of success. Process-orientated indicators make use of intermediate variables such as keeping appointment or pill counts to measure adherence [10]. Excellent adherence is one of the most important factors when it comes to treatment success.

Inadequate adherence increases the risk of drug resistance. In addition, treatment failure and increased hospitalisations intensify the risk of opportunistic infections. Virological failure is associated with suboptimal adherence levels. In a study by Kamya et al., investigating the predictors of long-term viral failure among Ugandan children and adults treated with ART, it was found that children were almost twice as likely to have viral failure compared with adults (26% vs. 14%; $P = 0.0001$) [11]. Adherence is seen as the most significant challenge to children receiving ART.

Reasons for this include the child's reliance on the caregiver, the nature of the medication and the child's reluctance to take medication on a daily basis.

It is noted in paediatric studies that adherence to ART in children is suboptimal, and relatively few estimates of adherence to ART have been published in children, especially in Africa. In an earlier systematic review by Vreenan et al., undertaken among a cohort of children in Western Kenya, adherence estimates ranged from 49% to 100% [12]. Simoni et al., reviewed fifty studies in the area of paediatric HIV infection, which revealed varying methods for assessing ARV adherence with a wide range of estimates of adherence. Estimates in this review varied widely from 20% – 100% [13].

Good adherence is a predictor of virological suppression and treatment success. Sub-optimal adherence may increase likelihood of drug resistance as well as increased risk of opportunistic infections. Adherences rates of more than 95% have been associated with virological suppression [14].

Measures of adherence to ART include caregiver self-report in the form of verbal recall, pill counts, diary records, plasma drug concentrations, as well medication event-monitoring systems. Drug monitoring in the form of viral load testing are thought to be more objective and yield better assessments, whereas methods such as pill counts and self-reporting tend to be less reliable and over-estimate adherence. Upon reviewing the literature, there is no 'gold standard' for the measurement of medication adherence in the paediatric population. In children, caregiver reporting is the most common method of assessing adherence.

Questioning that is structured and goal-directed is thought to yield accurate information about adherence [15].

In this prospective study, we used verbal recall as a measure of adherence. It is a method that can be used in a resource limited setting. It is commonly used in studies reporting adherence to ART in children. This measure reports a higher level of adherence than other methods [12]. In a study in Kampala by Nabukeera-Barungi et al., adherence in children using ART was measured using a three-day self-report, as well as clinic-based pill counts and unannounced pill counts. The three-day self-report of >95% adherence was 89.4%. Using clinic-based pill counts, 94.1% of children had >95% adherence to treatment compared with 72% by unannounced pill counts. This study was also in agreement that self-reporting over-estimates adherence by 20 – 25% [16].

In a study looking at adherence to ART in young children in Cape Town South Africa, methods such as medication return and caregiver report were used. This was a prospective study. Adherence by medication return was measured monthly. Adherence by questionnaire was measured after the child had completed three months of ART. Some 80% of the children obtained average medication return adherence of ≥90%. In terms of the use of the questionnaire, missing ≥ 1dose in the previous three days was present in 13.8% of children [17]. While this study demonstrated that good adherence is possible in young children using simple measures, it has to be viewed in the context that strict social inclusion criteria had to be met, which aided in improved adherence.

A cross-sectional survey was conducted in Mekelle, Ethiopia, by Eticha et al., looking at caregiver-reported adherence to ART among HIV infected children in two hospitals, from February to March 2013. A structured questionnaire was administered to caregivers to assess patient's adherence. The sample size comprised of 193 participants. Adherence assessment was based on caregivers self-reports in the past three and seven days prior to the interview. Participants who reported an intake of ≥95% of the prescribed medication were considered adherent and those with a reported intake of <95% were deemed non-adherent. Similar to our study, the questionnaire administered included the patient's demographic details, as well as the caregiver's details. In this study, adherence rates by caregiver reporting were 89.1% in the past three days and 83.4% in the past seven days before the interview [15]. While these rates are lower than that reported in our study, they are comparable to other studies conducted in Africa.

 Biressaw et al., also reported adherence rates comparing unannounced home-based pill count versus caregivers' report in 210 children between 1 December 2011 and 30 January 2012, on ART attending the paediatric ART clinic of Tikur Anbessa Hospital (TAH), Addis Ababa University. Caregivers were interviewed using a structured questionnaire. Caregiver-reported adherence was found to be 93.3% [18].

The adherence rates reported by caregiver self-report are shown in studies to possibly be over-estimated and higher than other methods. In a study by Vreeman et al., in a cohort of children on ART in Kenya, adherence rates with caregiver reporting was as high as 92%. They did note however that the caregiver reported adherence to study staff became less biased and more accurate as the study progressed.

Caregiver-reported adherence was found to be significantly higher than adherence by the medication event monitoring system (MEMS). There was poor agreement between caregiver-reported missed doses and MEMS [12].

There is a marked paucity of data in the body of literature describing adherence among children. In a qualitative systematic review published in Pediatrics, only eight studies, on a smaller scale, evaluated highly-active ART adherence interventions in children [13]. While caregiver reports were the least expensive and most widely-used methods, they did tend to overestimate adherence rates as compared to other methods. Caregivers were prone to recall bias. Self-reports among older children were noted to be subject to their cognitive abilities and developmental level. Children are cared for by many different caregivers. The guardian, grandparents or other family members may have incomplete information about the specifics of the medication given to the child and thus make reporting less reliable. The review concluded that future research should not only focus on evaluating the validity of self-report adherence measures—as these are practical and widely-used tools—but also compare this approach to other methods of assessing adherence in the paediatric population.

Our study is one of the few studies looking at adherence in a cohort of South African children. While most studies have been undertaken in the adult population on ART, our study utilised the method of verbal recall to assess adherence in a cohort of children in KwaZulu-Natal, South Africa. A high level of adherence was noted and suggests further studies need to be done in our setting to better assess adherence. Our study also reported on secondary factors associated with adherence, including

the role of the primary caregiver and the gender and age of the child. While these factors have also been reported on in previous studies, our work is unique in that little research has been done on treatment-naïve patients and follow-up undertaken. Our study had a long duration of follow-up over time so as to better-assess adherence over a prolonged period of time. The longer study period also allowed the assessment of change in adherence levels over the follow-up months and to identify possible reasons as to why patients were not adherent.

More novel ways of measuring adherence to ART in the paediatric population is for example by the Medication Event Monitoring System (MEMS). A prospective study of adherence in a paediatric HIV outpatient clinic in Cape Town, South Africa was conducted, assessing adherence using MEMS as well as caregiver self-reporting. The MEMS system comprised of pressure-sensitive microchip-equipped bottle caps which recorded the time and date of all bottle-opening events as presumptive doses taken by the patient. The data was stored in the chip and then downloaded to a computer and further analysed. In this study, Lamivudine and Abacavir syrup were used as MEMS monitored medication. In this cohort, median adherence by MEMS was 87.5%, and was found to be associated with virological suppression. Caregiver self-report adherence rate was 91%. This study concluded that MEMS was an accurate measure of adherence [19]. However, there were some limitations to this method. The bottles were not leak-proof and this made handling difficult. Second, the longer the caps were in use, the more syrup crystallised on the screw of the bottle neck and the cap, which made opening and closing of the cap tedious. Third, and more importantly, the cost of such a system is a significant limiting factor and may not be feasible in our setting.

In a study undertaken by Vreeman et al., looked at assessing adherence in children using the method of caregiver self-report, plasma drug concentrations as well as MEMS, median adherence by MEMS was reported to be 96.3%. Adherence estimates by caregiver report doses using the three-day and seven-day recall was 92%. This was similar to the adherence rates reported in our study. Of particular note, there was poor agreement between MEMS and other adherence measures (Kappa Statistics 0.04). In the above-mentioned study, Nevirapine and Efavirenz drug concentrations were taken at two time points (month 1 and month 4) during the study period. It was found that significant numbers of children had sub-therapeutic and supra-therapeutic drug levels. Sub-therapeutic levels are associated with drug resistance and virological failure. Drug concentrations did not correlate well with MEMS assessment of adherence due to several factors. Measuring these drug levels may not be a feasible option in a resource limited setting and may also be affected by several factors [12]. One strong criticism of this study is the lack of viral load testing which was stated as not being done due to financial constraints. Assessing viral load suppression is considered an important outcome in adherence to ART.

In an earlier study in a cohort of children of children in West Africa by Elise et al., an undetectable viral load was obtained for 55% of the patients with full adherence but for none of the patients with non-adherence (P = 0.098) [20]. Viral load testing is costly in resource-limited settings. Furthermore, obtaining blood samples in children is a challenge. While seen as an objective measure of adherence to ART, due to financial constraints, it was not a cost effective method of assessing adherence.

A secondary objective in our study was to examine factors associated with adherence outcome in young children. These factors include the socio-demographic background of the child and caregiver, regimen factors, as well as factors that are at an institutional level.

Age plays a role as a factor associated with adherence, and was one of the characteristics examined in this study. A very young child is totally dependent on her/his caregiver for the administration of medication. Toddlers and pre-school going children may refuse to take medication on an ongoing basis. School-aged children may develop the capacity to understand their disease process and the need for treatment. Adolescent children may find themselves missing medication in a bid to fit in, and there is the use of alcohol and drugs which may influence these processes. It is also a challenging developmental stage in a child's life. In a study in Harcourt, Nigeria, factors influencing adherence to ART were studied. It was found that children younger than five years of age (OR 2.62; 95%CI, 1.30-5.31) was a poor predictor of adherence. These children were found twice as likely to be non-adherent. Reasons for this include their dependence on an adult caregiver as well as the challenge of administering medication to very young children [21].

The role of the caregiver also plays a role as a predictor of adherence. Data are conflicting on the impact of the caregiver's biologic relationship to the child. The mother may be ill herself and have co-morbid illnesses. However, a biologic caregiver may have a better emotional connection with the child and consequently may be more motivated to promote good adherence compared with a non-biologic caregiver.

In cases of vertical transmission, where the biologic parents may have died or may be too ill to care for the child, the child then receives care from one or more relatives or guardians. In South Africa, there are many such examples of child-headed households and even grandmothers undertaking the role of primary caregiver to orphaned children. Loss of one or more parents is often complicated with mental health issues and multiple caregivers, all of which have been shown to influence adherence outcome. Adherence may be sub-optimal due to periods of disrupted routines, building of new relationship with the current-caregiver, as well as lack of disclosure, among other factors.

In the study in Nigeria, by Ugwu et al., the role of the primary caregiver was also examined. It was found that the mother being the primary caregiver was a predictor of poor adherence (OR 3.32; 95%CI, 1.33-8.67) [21]. A study in Abidjan, Côte d'Ivoire, describing the effect of ART in children revealed that the presence of multiple caregivers was associated with poor adherence [20].

Disclosure is also described in the literature as a challenge and a factor associated with adherence. Disclosure of the child's HIV status, as well as the caregiver's HIV status to family members can help both the child and parent/caregiver to receive support for adherence. However, stigma and discrimination possibly associated with disclosure are also perceived barriers to adherence. Accordingly, caregivers are reluctant to disclose a child's HIV status to anyone. Disclosure to children about their status and clinical condition is challenging. It often depends on the child's level of understanding. Disclosure of HIV status may help these children to understand their

illness better as well as their need for treatment and in so-doing increase their participation and responsibility for their treatment regimen. A study in Ghana, examining the prevalence and pattern of disclosure of HIV status in HIV-infected, found the prevalence of disclosure to be 21% in their cohort of children whose ages ranged between 8 – 14 years. It was also found that factors associated with disclosure include the age of the child, the level of education of child, administration of own HIV medications, as well as a longer period on HIV medication [22].

Some studies have shown male gender to be more associated with better adherence outcomes, while other studies have shown no significant association with adherence. One such study in Nigeria, in a cohort of children, describing adherence to ART, found that males were twice likely to adhere than females (odds ratio: 2.77; CI: 1.17-6.58) [21]. In a study held in Mulago Hospital, Kampala, Uganda, male gender was found not to be significantly associated with adherence rates [16].

Among other barriers to achieving optimal adherence include medication characteristics such as optimal dosage, pill burden, taste of medication and administering these to very young children. While syrups allow for proper dosing in young children, they can nevertheless be tedious to administer. ARV medications generally require frequent dosing and are supplied in formulations that may be difficult for children to tolerate. These can also be difficult to keep as some may require refrigeration, which in our setting, a number of poorer households may not have. Some ARVs need to be taken with food, so caregivers may have to perform the task of providing a meal and administering drugs simultaneously, assuming that an adequate supply of food is available. Additionally, caregivers may have difficultly

administering medication with a syringe [23]. Younger children may refuse to take medication due to taste. Gastro-intestinal side-effects may also hinder children taking medication and thus have an effect on adherence.

Other social barriers include poverty and food insecurity, especially in the setting of Sub-Saharan Africa. In South Africa, twelve million people live in extreme poverty. Many HIV-infected children live in poverty and are challenged by food insecurity and scarcity. These factors have been associated with poor adherence in developing settings [24]. Where primary caregivers to the child are living with HIV and AIDS and who themselves are poor, there is an increased risk of food insecurity. Food portions decrease as well as the quality and type of food. They may be ill and unable to attend work, thus limiting income and productivity. Furthermore, healthcare expenditures increase as well as the burden of caregiving. These households struggle to meet expenses and may also not make follow-up visits that have been scheduled. In a review article by Reda and Biadgilign describing determinants of adherence to ART, poverty was noted to be significant in the spread of HIV and AIDS as well as adherence. Parents who do not have food to administer with medication may not give the medication altogether. Of note, it was also reported that transportation costs were also seen as obstacles to taking ART. This resulted in loss to follow-up as well as affectation of adherence levels thereof [25].

The ART programme in South Africa has had dynamic changes over the years and more children are receiving ART. Furthermore, children are being tested more frequently and positive results detected timeously allow for treatment to be commenced much earlier in the disease process. Studies have shown that the

degree to which patients adhere to their regimen influences its success. Critically reviewing the studies carried out, it can be concluded that practical reliable measures of adherence can be used in resource-limited settings. Methods such as self-reports and diary records, although they tend to over-estimate adherence, are still considered to be cost-effective measures of adherence. However, there are limited studies that have effectively tested or compared these methods.

Several factors associated with adherence have been identified and examined in the literature. These include monitoring of adherence; clinical outcomes as well as factors associated with these will allow improvement in strengthening good clinical outcome for patients as well as a better patient and healthcare provider relationship. This will ultimately improve the quality of life of both children and caregivers. This has also paved the way for further research and development in the areas of adherence to ART in the paediatric population.

As mentioned previously there is no 'gold standard' for assessing adherence in young children, and hence this area of research needs to be further explored, especially in a resource-limited setting such as South Africa. The importance of adherence in this setting needs to be emphasised, in particular to caregivers.

Caregivers also need to understand the necessity and importance of regular follow-up visits as contact points to reinforce adherence. In our setting, loss to follow-up is a common occurrence. Perhaps studies undertaken should include a longer follow-up period to assess these further and provide recommendations for patients to keep follow-up visits so adherence can be examined on a longitudinal basis.

This secondary analysis will be reporting on a study carried out by Meera Chhagan, Shuaib Kauchali and Jan Van den Broek in 2012, and aims to shed light about adherence as well as factors associated with adherence.

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Chapter 2: A submission ready manuscript.

TITLE PAGE

Assessing adherence to antiretroviral therapy using the method of verbal recall in children from KwaZulu-Natal, South Africa

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABSTRACT:

Background:

Adherence to antiretroviral therapy is required for treatment success. Excellent adherence is one of the most important factors in determining treatment success and preventing viral resistance.

Objectives:

To describe reported adherence to antiretroviral therapy using the method of verbal recall, in a cohort of children in KwaZulu-Natal, and to look at possible factors associated with sub-optimal reported adherence.

Methods:

This was an analysis of a larger study which was undertaken at King Edward VIII Hospital, Durban, on children who were commencing antiretroviral therapy. This analysis assessed reported adherence using the method of verbal recall. A structured questionnaire was administered to care-givers to assess reported adherence.

Results:

The overall reported adherence rate in this study was 94 per cent. There was a substantial degree of agreement between verbal recall for the preceding week as well as since the last visit (k 0.64, p < 0.005). In a logistic regression analysis, children older than five years were less likely to report reported adherence (OR 0.871, 95 % CI 0.22-3.376). Females were twice as likely to report reported adherence as males (OR=2.05, 95% CI 0.49 -8.59).

Conclusion:

The prevalence of reported adherence to antiretroviral therapy in children, using the method of verbal recall, was found to be high in this cohort.

Introduction

The 2014 South African National HIV survey reported KwaZulu-Natal to have the highest prevalence rate of HIV infection, an estimated 16.9% [1]. There were an estimated 6,800,000 people living with HIV/AIDS in South Africa in 2014. Children (0-14years) were estimated at 340,000 [2].

The South African government approved the national roll-out plan for the "Comprehensive Care and Treatment for HIV and AIDS" in November 2003. This plan made provision for antiretroviral therapy (ART) within public sector facilities to persons with HIV-infection. ART in children has been shown to be effective in suppressing the virus, preventing opportunistic infections, and improving the well-being of children. Excellent adherence is one of the most important factors in determining treatment success and preventing viral resistance. The need for optimal adherence to lifelong therapy from an early age has been identified as a major challenge in the administration of ART to HIV-infected children [3]. At the Conference on Retroviruses and Opportunistic Infections (CROI) 2015, statistics revealed that almost half of all children and adolescents who were infected with HIV were not on treatment [4].

Children in low and middle income countries often face multiple and complex barriers to achieving optimal adherence. It is noted in paediatric studies that reported adherence to antiretroviral therapy in children is suboptimal, but relatively few estimates of adherence have been published [5]. Furthermore, assessing the level of adherence in children in a resource limited setting is also seen as a challenge.

Methods such as self-report, diary records and pill counts have been used. Care-giver self-report as a measure of reported adherence may be seen as subjective and over-estimating adherence. Studies have shown that self-reporting over-estimates adherence by 20-25 per cent **[6, 7]**. However, in a resource limited setting, self-report as a measure of reported adherence can be viewed as a cheap and practical method **[8]**.

A more novel way of measuring adherence to ART in the paediatric population is by the Medication event monitoring system (MEMS). In one such study, at an academic hospital in Cape Town, young children with a mean age of 51 months were investigated. Reported adherence was monitored electronically over three months, and viral loads were evaluated pre- and post-study. Whilst MEMS may be an objective method of measuring adherence, it may not be as cost effective as care-giver self-report, diary records or pill counts in a resource limited setting **[9]**.

There are few studies in children using viral load testing to assess suppression **[10]**. Available studies in children show rates of suppression to be between 27% and 75%. In one South African study, virological suppression was lower in children less than two years of age. The method of viral load testing as a marker to assess reported adherence is a part of routine care and management. There are initiatives by many countries and international donor bodies to roll out affordable viral load testing in poorer, less-resourced countries **[4, 10]**.

Factors associated with poor adherence in children, include whether the mother is the primary caregiver and whether psychosocial factors, medication regimens, financial burden due to expenses incurred on her own therapy, impact on the child's therapy **[11]**. The youngest children are most likely to be lost to follow-up. Individual patient barriers include low socio-economic status, lack of disclosure and low

parental education. Structural barriers include distance to treatment facility **[12]**. In contrast, some factors promoting reported adherence include family support, disclosure and frequent follow-up **[7, 11]**. In South Africa, there is a high burden of disease and co-infection with tuberculosis and HIV. This co-infection also contributes to sub-optimal reported adherence. Drug factors such as taste and side-effects may also significantly alter adherence levels **[13]**.

This study was a secondary analysis looking at reported adherence in children in a resource limited session using the method of verbal recall as well as factors associated with reported adherence **[14]**.

Aims and objectives

The primary aim of the study was to evaluate reported adherence to ART in children. A secondary aim was to look at factors which might impact on reported adherence.

Methods

Study population and design

This study was an analysis of data from a prospective study entitled "Metabolic and Nutritional effects of anti-retroviral therapy in children. PI: M Chhagan". The parent study was conducted in an urban hospital, King Edward VIII hospital, in Durban, Kwa-Zulu Natal, in a cohort of children commencing ART **[14].** Only the participants who were treatment naïve at the time of initiation were considered for enrolment in this study. Participants who had a willing parent or guardian to give informed consent and to comply with the study schedule were included.

These participants were identified through the PMTCT programme or referred from public clinics in areas such as Cator Manor, as well as hospitals beyond the catchment area which included Addington Hospital. Eligible participants for the study were identified, recruited and informed consent obtained by study staff.

Eligible participants scheduled to commence ART were informed of the reported adherence sub-study.

Inclusion criteria were: children who were commencing ART, treatment naïve at the time of initiation, females below 11 years, and males below twelve years, who did not exhibit secondary sexual characteristics. This age group was chosen as females more than 11 years and males more than twelve years are generally considered to be adolescents. Participants had to have a willing parent or guardian to give informed consent and be able to comply with the study schedule. Those children who did not meet above criteria were excluded.

Method of data collection

Data collection was done using baseline and follow-up structured questionnaires directed at the primary caregiver. Information was collected by research staff. The baseline and follow-up questionnaires were in written format. It was available in the English language. It was designed for this particular study. Each child underwent a detailed clinical assessment by a research doctor prior to and during treatment. Baseline clinical characteristics of the cohort included demographic details such as age, gender, primary caregiver, recent hospitalisations and illnesses, age of co-trimoxazole prophylaxis initiation, as well as tuberculosis infection history. This information has been previously published by Chhagan et al. **[14].**

Maternal details were also enquired about, including whether the mother was alive, age, history of tuberculosis, if mother/primary care-giver was taking antiretroviral therapy, as well as any illnesses in the preceding three months. Other variables assessed were whether the mother received antiretroviral therapy or nevirapine during pregnancy as well as whether the baby had received nevirapine as part of prevention of mother to child transmission.

Clinical assessment included WHO staging, enquiring about side-effects and grading severity, baseline blood investigations including CD4 count, viral load, and biochemistry tests **[14].**

The follow-up questionnaire at 1, 3, 6, 9, 12, 18, and 24 months of the study period looked at reported adherence details using the method of verbal recall in the form of treatment doses/days missed in the past week and since the last visit. If the answer to those questions were "yes", then the treatments doses/days missed were recorded as well as reasons for the missed doses/days.

Additional information in the follow-up questionnaire included recent illnesses, hospitalisations, current treatment, side-effects and whether the patient was taking other medication.

Ethical considerations

Ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal for the parent study (Ref: E181/05). The KwaZulu-Natal Department of Health and medical management of King Edward VIII Hospital granted permission for conduct of the study. This study is an analysis of an existing database and did not entail any contact with participants.

Results

The data collected from the responses was analysed with SPSS version 23.0. Statistical significance was set at a p value < 0.05. From September 2006 to July 2009, 165 patients were screened at King Edward VIII hospital. A total of 151 children were eventually recruited. Demographical data are presented in Table 1.

Overall, the ratio of males to females is approximately 1:1. Children older than five years of age comprised 48.4% of the cohort. The primary caregiver was the biological mother in 73 (49%).

The mean reported adherence for the preceding week was 94%. The mean reported adherence for the recall since last visit was 95.4 per cent. These were calculated as a percentage of the number of doses taken divided by the number of expected doses in the preceding week and since last visit respectively. There was a substantial degree of agreement between verbal recall for the preceding week as well as the last visit (k 0.64, $p<0.005$). (Figure 1)

Reported adherence was also compared as a measure over time and was shown to improve from the first month onwards. Various reasons were cited for non-adherence. These included forgetting to take medication, early trip to hospital; social circumstances such as a death in the family, primary care-giver demised, and drug side-effects. One of the reasons also included was a hospital strike. Figure 1 refers to the reasons for missing doses as described with percentages.

A logistic regression model was used to predict a dichotomous categorical variable from a set of predictor variables (Table 2.)

Children who were older than five years of age were found to be less adherent to antiretroviral therapy (OR=0.87, 95% CI 0.25-3.33), and males were found to be less adherent than females (OR=2.05, 95% CI 0.49 -8.59). The mother being the primary care-giver was not associated with reported adherence, (OR=0.72, 95% CI 0.18-2.92).

Discussion

Adherence to ART in children is critical to maximise the success of the drugs. Inadequate adherence results in virological and immunological failure. In this study,

verbal recall over the past week as well as since the last visit found reported adherence rates of 94 and 95.4 per cent respectively. The overall reported adherence rate was 94 per cent. This is similar to adherence rates reported in similar studies in African countries **[6]**. The method of verbal recall may overestimate reported adherence levels and could reflect bias from using a caregiver's report, such as social desirability bias or recall bias. Of note, is the improved reported adherence over time, which could be as a result of enforcing the need to take medication on time and the importance of not missing doses. However, verbal recall in a resource-limited setting may be an important method of reported adherence support.

The main reasons given for missed doses included care-giver forgetting, early trip to hospital, and death in family as well as side effects. One particular reason cited was a hospital strike. These factors represent socio-economic, medication-related and health-care related challenges as possible barriers to reported adherence, identified in other studies too **[13]**. In a study in KwaZulu-Natal, South Africa, reasons reported for missed doses were: financial barriers that prevented caregivers from collecting medication on time, side-effects, incorrect dosing by a caregiver, missed follow-up visits and pharmacy collections, confusion as well the child refusing to take medication **[15]**.

Factors associated with reported adherence in this study included the age of the child, who the primary care-giver was, as well as the gender of the child. Children older than five years of age, and male gender, were found to have less increased likelihood of reported adherence, and this has been shown in reports from other studies **[13]**. In this study, the primary care-giver was not found to be statistically significant in influencing reported adherence outcome. In a study by Ugwa R et al,

children with mothers as the primary caregiver were three times more likely to be non-adherent. Reasons for this included the mother having poor health, as well as lack of disclosure. This would mean that there would be no one else to administer medication if the mother was ill **[16]**.

There were some limitations to the study namely methods of verbal recall possibly over-estimate reported adherence. In addition, the social criteria used to determine ART eligibility may have further selected those patients more likely to be adherent. The importance of measuring reported adherence to ART in children is to improve overall well-being and longevity in patients as well as preventing opportunistic infections.

Conclusion

This study revealed the prevalence of reported adherence using the method of verbal recall over the past week as well as since the last visit to be 94 per cent and 95.4 per cent respectively. This is comparable to reported adherence rates using the method of verbal recall in similar studies. Verbal recall tends to over-estimate reported adherence, as demonstrated in other studies as well. However, in a resource-limiting setting, this may be seen as a measure of reported adherence to improve outcomes over time. Further studies in the paediatric population are needed to assess reported adherence and interventions thereof to improve outcomes.

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LEGEND TABLES:

Table 1. Children's demographic characteristics

Table 2: Factors associated with reported adherence

LEGEND FIGURES:

Figure 1.Reported adherence over the follow-up periods

Figure 2. Reasons for missing doses

Table 1. Children's demographic characteristics

Characteristics		Frequency (%) *n* = 151
Gender	Male	77 (51)
	Female	74 (49)
Age (years)	< 2	41 (27.7)
	2-5	37 (24.5)
	>5	73 (48.4)
Primary care-giver	Mother	73 (48.3)
	Other	78 (51.7)

Table 2: Factors associated with reported adherence

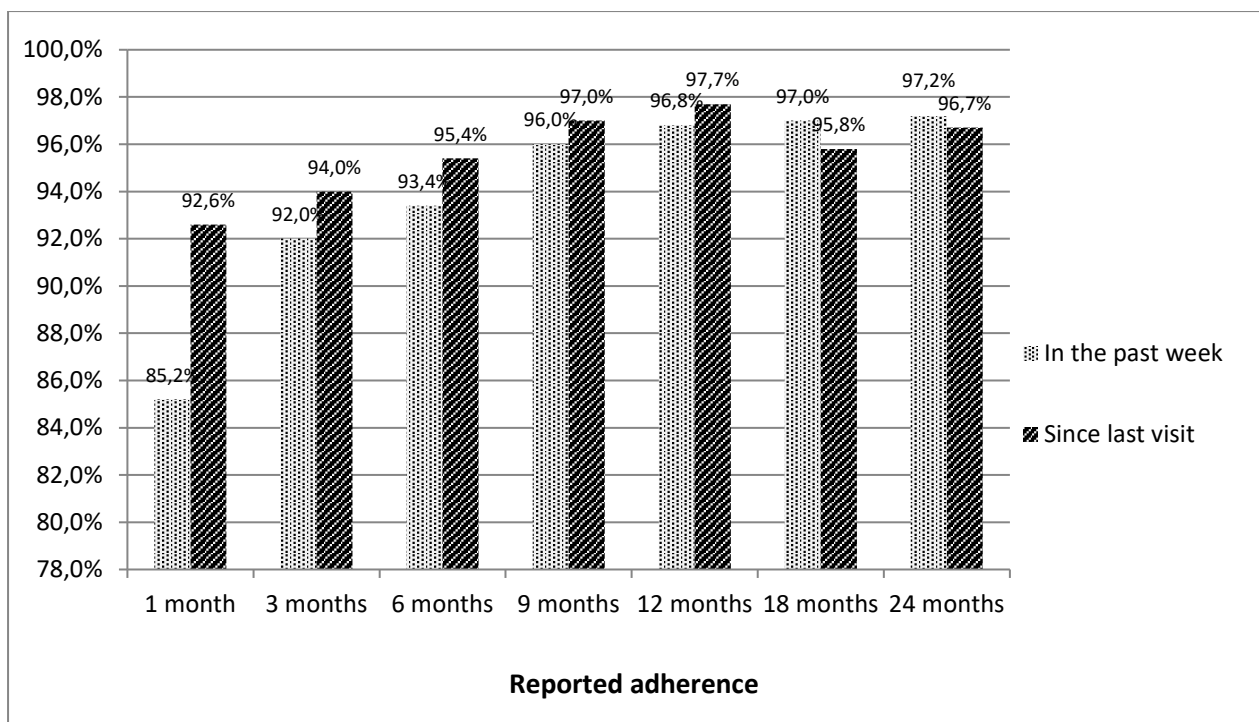| Factors	Reported adherence outcome		OR (95%CI)	P value
	Adherent n = 142 (%)	*Non-adherent* N = 9 (%)		
Age of child				
<2	38 (92.6)	3 (7.4)	0.73 (0.18 - 3.07)	0.79
2-5	35(94.6)	2(5.4)	1.2 (0.24 - 5.98)	
>5	69 (94.4)	4 (5.6)	0.87 (0.25 - 3.38)	
Gender of child				
Male	71 (95.9)	3(4.1)	2.05 (0.49 -8.59)	0.65
Female	71(92.6)	6(7.8)		
Primary caregiver				
Mother	68 (93.2)	5 (6.8)	0.72 (0.18 -2.92)	0.32
Other	74 (94.9)	4(5.1)		

Figure 1.Reported adherence over the follow-up periods
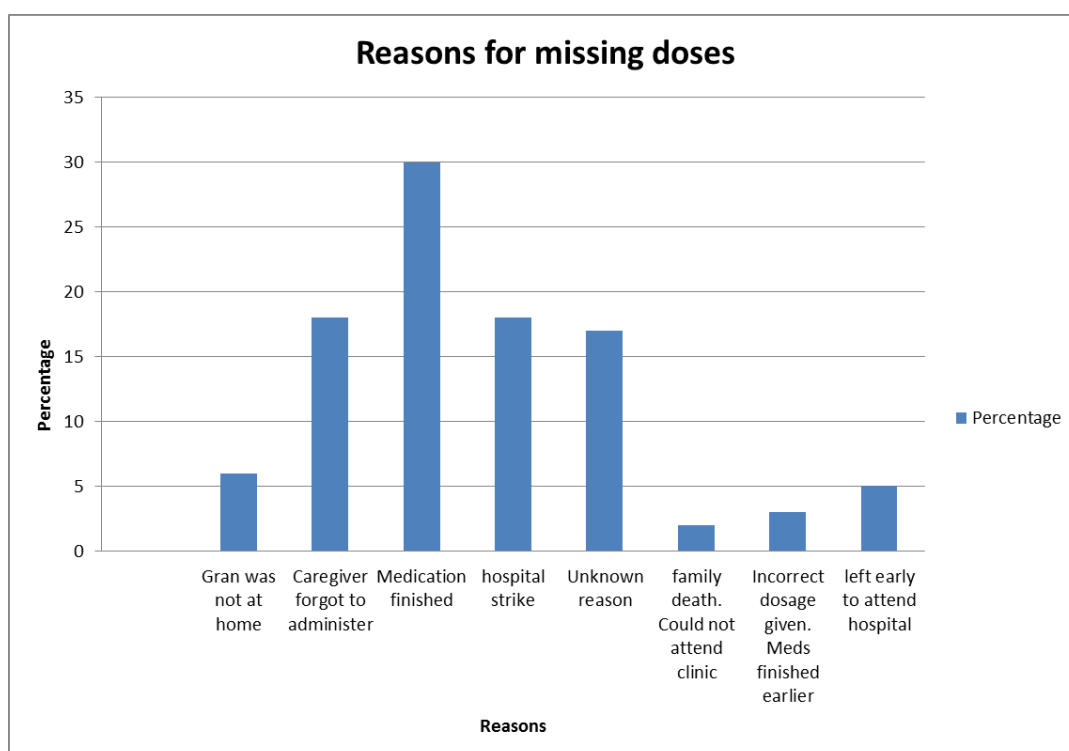

Figure 2. Reasons for missing doses

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)

Title of the study

Adherence to Antiretroviral therapy in children using the method of verbal recall

Aim of study

The aim of the study is to evaluate adherence to HAART in children using the method of verbal recall over the preceding week, as well as since the last visit. The study will be a secondary analysis of data from a prospective study entitled Metabolic and Nutritional effects of antiretroviral therapy in children. PI: M Chhagan, Paediatrics, BREC Ref: E181/05 that used verbal recall and diary records to describe the adherence to HAART, in a resource limited setting. A secondary aim would be to look at factors associated with adherence.

 Specific objectives

•   To compare adherence to HAART in children from other studies with this study

•   To describe the difficulties associated with adherence to HAART in the paediatric population

•   To analyse data from a prospective study of a cohort of children that used verbal recall in predicting adherence to HAART

•   To identify factors associated with suboptimal-adherence

Background and literature

Approximately 85% of the 2.3 million HIV-infected children under 15 years worldwide live in sub-Saharan Africa (Davies, Boulle, Fakir, Nuttall, & Eley, 2008). Antiretroviral therapy in children has shown to be effective in suppressing the virus, preventing opportunistic infections, and improving the well-being of children and adults world-wide.

Adherence is the process or condition of adhering. Adhering means to be devoted, be a follower or to follow closely. Excellent adherence is one of the most important factors when it comes to treatment success. Adherence to lifelong therapy however, in children, in a resource limited setting has been identified as a major challenge (Davies et al., 2008). Factors such as volume, taste, intake of drugs, dosage intervals and side effects play a role in the outcome of adherence to antiretroviral therapy in children (Iroha, Esezobor, Ezeaka, Temiye, & Akinsulie, 2010).

It is noted in the paediatric studies that adherence to antiretroviral therapy in children is suboptimal, and relatively few estimates of adherence to antiretroviral therapy have been published in children. Furthermore assessing the level of adherence in children, in a resource limited setting is also seen as a challenge (Steele & Grauer 2003). Methods such as self-report, diary records and pill counts have been used to measure adherence.

In a study looking at adherence to antiretroviral therapy in young children in Cape Town South Africa, methods such as medication return and care-giver report were used. This was a prospective cohort study. Adherence by medication return was measured monthly. Adherence by questionnaire was measured after the child had completed three months of antiretroviral therapy. Eighty per cent of children obtained average medication return adherence of ≥90 per cent. In terms of the use of the questionnaire, missing ≥ 1dose in the previous three days was present in 13.8 per cent of children. Whilst this study demonstrated good adherence is possible in young children using simple measures, it has to be viewed in the context that strict social inclusion criteria had to be met, and this aided adherence to be quite good.

Care-giver self-report as a measure of adherence may be seen as a subjective method, over-estimating adherence. Studies have shown that self-reporting over-estimates adherence by 20-25 per cent (Nabukeera-Barungi, Kalyesubula, Kekitiinwa, Byakika, & Musoke, 2007). However, in a resource limiting setting, self-

report as a measure of adherence can be viewed as a cost-effective and practical method.

In a study in Kampala (Nabukeera-Barungi et al., 2007), adherence in children using antiretroviral therapy were measured using a three day self-report, as well as clinic based pill counts and unannounced pill counts. The 3-day self-report of >95% adherence was 89.4%. Using clinic-based pill counts, 94.1%, had >95% adherence to treatment compared with 72% by unannounced pill counts. Pill counts can be seen as an objective method to measure adherence to ART in children.

In addition, more novel ways of measuring adherence to ART in the paediatric population is for example, by Medication event monitoring system (MEMS). In one such study, at an academic hospital in Cape Town, young children with a mean age of 51 months (SD 25.6) were investigated (Muller, Bode, Myer, Stahl, & von Steinbuchel, 2011). Adherence was monitored electronically over three months, and viral loads were taken pre- and post-study. Whilst MEMS may be an objective method of a measure of adherence, however, in a resource limited setting, it may not be as cost effective as care-giver self-report, diary records or pill counts.

It is also possible that different adherence measures might complement each other, and increase their sensitivity. Giordano et al found close correlation between various adherence measures in adults.

The principal questions that need to be asked, reviewing the literature, revolve around the above-mentioned measures of adherence, their sensitivity and use in a resource-limited setting. Adherence of > 95% seems necessary to achieve viral suppression and to avoid development of viral resistance (Friedland GH and Andrews LA; 2011).

It is established that success of HAART rests on a high level of adherence to the medication, and centres offering HAART services are required to assess the level of individual patient adherence (Hardon, Davey, Gerrits, Hodgkin, Irunde, Kgatlwane et al., 2006). For HIV-positive children, sustaining adherence is even more challenging.

There has been an up-scaling of the ART program for HIV-infected children in resource-limited settings. Studies have shown that the degree to which patients

adhere to their regimen influences its success. Critically reviewing the studies carried out, it can be concluded that practical reliable measures of adherence can be used in resource limited settings. Methods such as self-report and diary records, though they tend to over-estimate adherence, are still considered to be cost effective measures of adherence. However there are limited studies that have effectively tested or compared these methods. Noteworthy there is a need for a study to be carried out to test and measure adherence in children in KZN, South Africa. This study will be reporting on a study carried out by Meera Chhagan, Shuaib Kauchali and Jan Van den Broek in 2012.

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Study design

Study population

The parent study Metabolic and Nutritional effects of antiretroviral therapy in children. PI: M Chhagan, Paediatrics, BREC Ref: E181/05 was carried out at King Edward VIII hospital Durban, in a cohort of children commencing HAART. Inclusion criteria were children commencing HAART, females below the age of eleven years, and males below the age of twelve years, who did not exhibit secondary sexual characteristics. Only the participants who were treatment naïve at the time of initiation were considered for enrolment in the study. Importantly, participants who had a willing parent or guardian to give informed consent and to comply with the study schedule were included. A cohort of 151 participants was enrolled into the study. Age of the participants ranged from 6.9 to 159.3 months.

Sampling strategy

The parent study Metabolic and Nutritional effects of antiretroviral therapy in children. PI: M Chhagan, Paediatrics, BREC Ref: E181/05, recruited participants between September 2006 and July 2009, who were commencing HAART at King Edward VIII hospital, in Durban, Kwa-Zulu Natal. These participants were encountered through the PMTCT programme or referred from various hospitals. Eligible participants for the study were identified, recruited and consented by study staff. Eligible participants scheduled to commence HAART were also informed of the study.

Inclusion/exclusion criteria

Inclusion criteria were:

- Children who were commencing HAART

- Treatment naïve at the time of initiation

- Females below 11 years, and males below twelve years, who did not exhibit secondary sexual characteristics.

- Participants had to have a willing parent or guardian to give informed consent and able to comply with the study schedule

Exclusion criteria:

- Children who had already commenced HAART

- Post-pubertal males older than twelve years of age

- Post-pubertal females older than eleven years of age

- Participants who did not have a willing parent/guardian giving informed consent and not able to comply with study schedule were excluded from participating in the study

Data collection methods and tools

Participants were assessed at baseline, and were followed up at 1, 3,6,9,12,18 and 24 months after the initiation of HAART. A structured follow up assessment form was used to record various details including maternal and child details, examination findings, current investigations as well as adherence details. Adherence to HAART was assessed using care-giver verbal recall, diary records, as well as pill counts at each visit. For verbal recall, participants were asked about treatment days missed in the preceding week, as well as treatment days missed since their last visit. If the

answers were yes to these questions, the number of days missed were recorded, with reasons.

Statistical planning

Predictor variables for the analysis in the proposed MMed study will be adherence and non-adherence, measured by verbal recall in the past week as well as since the last visit. These will be used to create categorical variables (outcome is either adherent or non-adherent). Adherence will be ascertained on follow-up assessment of patients.

Independent variables will include child factors such as age, gender as well as number of hospitalisations before starting HAART.

Caregiver factors in this study will include relationship to the child such as if the mother is the primary care giver, if the caregiver is also receiving ART, and recent illnesses of the mother.

Drug factors that will be assessed are side effects of medication and if there are any additional medication taken (these included nutritional supplements and over the counter medication).

Sample size

In the parent study, Metabolic and Nutritional effects of antiretroviral therapy in children. PI: M Chhagan, Paediatrics, BREC Ref: E181/05, 154 were deemed eligible for the study, however, 151 participants were enrolled. This cohort included 74 females and 77 males. Six children had died during follow up, and thirteen were lost to follow up. Eleven children were transferred to other treatment sites for continuation of treatment, mainly due to residential proximity.

Data Analysis

Adherence to ante retroviral therapy was assessed using the method of verbal recall. A structured follow-up assessment was used to assess adherence to antiretroviral therapy in participants, in addition to maternal and child details, as well as examination findings and investigations.

Children were followed up monthly for three months, then 3 monthly until 9 months, thereafter 6 monthly until 24 months.

Adherence proportions (and associated 95% confidence intervals) was calculated for each follow up time period to assess temporal changes in adherence patterns. A Chi-squared test for trend will be used to detect with a significant decrease in adherence occurs over the follow up period.

Predictor variables in this study will be adherence and non-adherence, measured by verbal recall over the past week and last visit.

For verbal recall, adherence was assessed by asking participant's caregiver number of treatment days missed in the past week, as well as last visit. The options being a "yes/No" answer to these questions. If the answer was "yes", the number of treatment days missed was recorded. Adherence was defined as having taken all doses of the ARVs during the past week, as well as since the last visit. If more than one treatment day had been missed, then this would be defined as non-adherence. Thereafter the percentage of participants that were adherent was measured using a dichotomous variable for adherence.

The main outcome variables in this study will be adherence and non-adherence, measured by verbal recall over the past week and last visit.

Adherence proportions (and associated 95% confidence intervals) will be calculated for each follow up time period to assess temporal changes in adherence patterns. A Chi-squared test for trend will be used to detect with a significant decrease in adherence occurs over the follow up period.

Most care-givers are likely to report adherence as opposed to non-adherence. Therefore, a comparison of the method of verbal recall over the past week versus

last visit will be made, to determine which method is likely to report non-adherence. The agreement between the two methods will be analysed by McNemar's test.

The Kappa statistic will be used to assess the pairwise agreement between verbal recall over the past week versus last visit. The following has been proposed as a general standard for assessing the strength of agreement for the kappa coefficient: ≤0 poor, .01–.20 slight, .21–.40 fair, .41–.60 moderate, .61–.80 substantial, and .81–1 almost perfect [Landis and Koch, 1977].

Factors associated with non-adherence will be assessed using bivariate logistic regressions. These will include independent variables of child factors such as age, gender as well as number of hospitalisations before starting HAART. Factors associated with a discordant outcome with a p-value cut-off <0.2 based on the bivariate associations will be selected for entry into an adjusted multivariable logistic model. Significance in the adjusted model will be assessed at p<0.05. Model diagnostics (assumptions, fit, influential observations) and predictive qualities (sensitivity, specificity, positive predictive value [PPV]) will be assessed.

Caregiver factors/variables in this study will include relationship to the child such as if the mother is the primary care giver, if the caregiver is also receiving ART, and recent illnesses of the mother.

Drug factors assessed will be side effects of medication and if there would be any additional medication taken (these included nutritional supplements and over the counter medication).

Study location

King Edward VIII hospital, in Durban, Kwa-zulu Natal, South Africa

Study period

Between September 2006 – July 2009

Limitations to the study

- In this study, methods of verbal recall may over-estimate adherence

- The social criteria used to determine ART eligibility may have further selected those patients more likely to be adherent

- Regular monitoring of adherence in this study may enhance adherence levels, and not give a true picture of adherence in the general paediatric population

Ethical considerations

The parent study, conducted by Principal Investigator Dr Chhagan had full approval by the Ethics review Committee of the University of Kwa-Zulu Natal Brec ref: E181/05. The MMed study is a secondary analysis of existing data and does not entail any contact with participants. The PI will provide a de-identified dataset for the MMed analysis. Permission was granted by the Kwa-Zulu Natal Department of health as well as the management of King Edward VIII Hospital for the study to be undertaken.

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Find attached

Appendix 3: Ethical approvals

Find attached

Appendix 4: Data collection tools (for example)

Find attached