

ADHERENCE TO ANTIRETROVIRAL THERAPY IN CHILDREN IN ZIMBABWE: A
RANDOMIZED CONTROL TRIAL TO VALIDATE A NEW SELF-REPORTED
ADHERENCE MONITORING TOOL

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ABSTRACT

Background

Among children taking antiretroviral therapy (ART), self-reports have been widely reported to over-estimate adherence levels. Pill count adherence levels are often lower than self-reported levels, with unannounced home pill count adherence being lower than facility based pill count adherence. There is often poor agreement between pill count adherence levels and those measured using other objective adherence measuring methods such as Medication Event Monitoring Systems (MEMS[®]), which is widely viewed as the gold standard for adherence measurement.

Objectives

The aim of this study was to design and evaluate a new self-reported paediatric adherence monitoring tool, assess the feasibility of using pill count methods in monitoring adherence and identify challenges to reporting adherence among children on ART in rural and urban Zimbabwe.

Methods

A dual centre, superiority, parallel design RCT was conducted to evaluate the newly-developed visually- and verbally-cued ‘past 10 days’ tool for the assessment of adherence in children on ART at two sites in Zimbabwe; Harare Central Children’s Hospital in an urban setting, and Murambinda Mission Hospital, a rural site. Child-caregiver pairs presenting to one of these facilities for the child’s review of ART and refill of the medication were recruited, signed informed consent obtained, and were randomised for self-reported adherence monitoring into either the experimental group (‘new 10-day tool’) or the control group (‘PACTG-style’ self-report tool). Data (demographic, socioeconomic, and reported adherence) were collected in individual interviews with child-caregiver pairs. Additional adherence monitoring methods used for both groups included the Morisky-8-Item Medication Adherence Scale (MMAS-8) and a facility based pill count. FGDs were held with groups of caregivers and groups of children ≥ 13 years of age to understand reasons for non-adherence as well as issues around reporting non-adherence.

Superiority testing was conducted by comparing adherent proportions and their confidence intervals (95% CI). Further concurrent validity test was done using the Mann-Whitney U test to evaluate the relationship between the new tool and the MMAS-8 scores. Agreement

between the child and caregiver reports of adherence was used as a test of reliability of the new tool using the kappa statistic. Socio-demographic, clinical and care-related factors associated with adherence were identified using reported adherence in both child and caregiver groups in a logistic regression model. Two pill count methods were assessed for feasibility using the proportions of children with complete data for calculating adherence levels, and their CI and a comparison of the two methods, a routinely-used method and one that incorporated the reported residual quantity (RRQ) of medication at last refill.

Results

Analysis included 245 child-caregiver pairs, 123 in the experimental group and 122 in the control group. The median age for children was 9 years. In the experimental group, adherence by caregiver and child reports ranged from 94.3% - 98.4% and 78.4% - 96.1%, and those in the control group ranged from 89.2% - 97.5% and 71.2% - 98.1%, respectively. There was no significant difference between adherence levels in the two groups. Adherence levels measured by both the experimental and control tools were found to be associated with MMAS-8 adherence levels ($p < 0.05$). Agreement between child- and caregiver-reported adherence was moderate though significant (kappa; 0.407, $p < 0.05$). Only about half of the children had adequate data to compute pill counts. Proportions adherent at 95% cut-off were 39% by the 'routine pill count' and 58% by the 'Pill count RRQ'.

Being an orphan was associated with child reported-adherence whereas use of non-human reminders, having a maternal relative as a primary caregiver and knowledge of dose frequency, were all associated with caregiver-reported adherence. Major causes of non-adherence mentioned during the FGDs included interference of medication administration times with scheduling of routine socio-economic activities and lack of support from some non-biological caregivers. Reporting of non-adherence appeared to be hampered by perceptions of negative reactions by healthcare workers to these reports and by caregivers being unaware that the child missed some doses.

Conclusions

The 'new 10-day tool' was not shown to be superior to the 'PACTG-style tool' in detecting non-adherence, however this new tool was found to be a valid and reliable adherence monitoring tool that included a moderately long recall period of 10 days, can be applied without the need for the respondent to remember names of individual medicines in the

regimen, and can capture information on non-adherence resulting from taking partial doses. The pill count method was associated with a number of problems connected to accurate return of medication to the facility and availability of information to compute pill counts. Challenges to reporting non-adherence are more related to social desirability bias and caregiver misinformation than to failure to recall incidences of missed doses.

Recommendations for practice

Healthcare providers must be trained and encouraged to recognise that reliance on self-reported adherence in monitoring patients on ART requires that these reports should be accurate. Therefore every effort must be applied to creating an environment that minimises barriers to reporting non-adherence, such as provider anger or judgemental attitudes, and that encourages patients to report non-adherence behaviour. Healthcare providers must record complete dispensing information such as date of dispensing and quantity of each medication in order to facilitate the computing of pill count adherence levels.

Recommendations for further research

Further research should focus on designing and testing a pill count adherence tool that enables the clear, continuous recording of information required for computing pill count adherence data. Identification of causes of both shortfalls as well as excesses in pill counts in medication returned to the health facility should be researched in settings similar to those for my study. The quality of the patient-provider relationship demands further research in Africa, and should investigate barriers and facilitators to open, two-way communication in an attempt to improve the accuracy of self-report methods.

Key Words

Adherence, monitoring, tools, self-reports, pill count, children, HIV, ART, feasibility, reliability, LMIC, Zimbabwe

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DEDICATION

This thesis is dedicated to the first HIV-infected child I saw in 1991 in Ward A4 at Parirenyatwa Hospital, Harare, who was a failure to thrive due to AIDS, and to all children worldwide who, whilst young and innocent, suffered from a condition that is otherwise preventable, mainly by being faithful to one faithful partner.

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LIST OF ACRONYMS

24RI	24-hour Recall Interview
AACTG	Adult AIDS Clinical Trials Group
ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
CD4	Cluster of Differentiation 4 T-helper Cell (CD4 lymphocyte)
FDCs	Fixed-Dose Combinations
FGDs	Focus Group Discussions
HAART	Highly Active Antiretroviral Therapy
HIC	High-Income Countries
HIV	Human Immunodeficiency Virus
LMIC	Low- and Middle-Income Countries
MEMS [®]	Medication Event Monitoring Systems
MoHCW	Ministry of Health and Child Welfare
MMAS-8	Morisky-8-Item Medication Adherence Scale
MTCT	Mother to Child Transmission of HIV
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
OI	Opportunistic Infection
PACTG	Paediatric AIDS Clinical Trials Group
PCR	Deoxyribonucleic Acid (DNA) Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission of HIV
RCT	Randomized Control Trial
RQ	Residual Quantity
RRQ	Reported Residual Quantity
SADC	Southern African Development Community
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
VAS	Visual Analogue Scale
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1 Background

The thesis focuses on the accuracy of self-reported adherence and pill count methods, two adherence monitoring methods that are routinely used in clinical settings in resource-constrained settings, and on levels of adherence to antiretroviral therapy (ART) in children in Zimbabwe. The research addresses some of the gaps in understanding and monitoring of adherence to ART among children receiving services in resource-constrained settings of Zimbabwe.

With an approximate 2.3 million people having become newly infected with human immunodeficiency virus (HIV) globally in 2012 and an estimated 1.6 million people dying of Acquired Immunodeficiency Syndrome (AIDS) in the same year, ART remains one of the major interventions to fight the HIV pandemic and reduce the impact of HIV and AIDS (UNAIDS 2013b). There has been a significant decrease in the number of people dying from AIDS from the peak in 2005 when an estimated 2.3 million people died from the same cause. The decrease is mainly ascribed to scale-up of HIV treatment services (UNAIDS 2013b).

Despite efforts to prevent mother-to-child transmission (MTCT) of HIV, AIDS-related deaths among children remained high with 260 000 children dying of AIDS globally in 2009 alone (UNAIDS 2010). Nevertheless, the number of new HIV infections among children reduced by 35% between 2009 and 2012 (UNAIDS 2013b). Increasing ART coverage to extend these life-saving drugs to children has presented many challenges.

For those children who do manage to access ART, interventions to improve the effectiveness of treatment are critical. Treatment adherence monitoring and support are among key elements for a successful ART programme as highlighted in the World Health Organisation (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) Treatment 2.0 document, that describes an approach to ART that simplifies treatment and hence scale-up of these services (UNAIDS 2010).

Amidst intensified efforts to reduce MTCT of HIV in Zimbabwe, there were 15 000 reported new paediatric HIV infections in the country in 2011, a decline from 21 000 in 2009

(UNAIDS 2013a). At the end of 2009, national ART coverage remained low in children (30%) compared to adults (52%), based on the WHO 2006 guidelines (UNAIDS 2010). With the newer WHO guidelines of 2010 and 2013 which advocate for the initiation of ART at earlier stages of the HIV disease (World Health Organization 2010b, World Health Organization 2013), and therefore increase the number of children eligible for treatment, ART coverage in children is even lower.

ART in children initially faced the challenge of shortages of both expertise in managing paediatric ART as well as availability of suitable dosage forms for the very young children (Chima 2007). According to the Zimbabwe Ministry of Health and Child Welfare (MoHCW) (now Ministry of Health and Child Care) National Opportunistic Infections (OI)/ART Report (Ministry of Health and Child Welfare, Zimbabwe 2008b), access to definitive diagnosis of HIV among children below the age of 18 months was limited. All these factors resulted in delayed access to ART by the younger children. During the ART rollout period in Zimbabwe in 2008, there were fewer sites initiating paediatric ART than adult ART, resulting in a disproportionately lower coverage of ART for children (Ministry of Health and Child Welfare, Zimbabwe 2008b). This meant that some children and their caregivers had to travel further than adults to access ART with an anticipated negative impact on adherence to treatment.

Since 2004, there has been a rapid scale-up of ART services in Zimbabwe, from seven ART-initiating sites in December 2004 to 107 sites by December 2008 (Ministry of Health and Child Welfare, Zimbabwe 2008b), accompanied by an increased demand created through the provider-initiated counselling and testing approach (Mugore et al. 2008). This rapid expansion of ART services was accompanied by programmatic concerns about HIV drug resistance among the general population on ART (Ministry of Health and Child Welfare, Zimbabwe 2009a). Dr Apollo, the ART coordinator in the AIDS and Tuberculosis (TB) unit of the MoHCW, stated in a formal conversation held on the 5th of February 2009 that no published reports on research on adherence to ART in children had been made available to the decision-makers at the MoHCW concerning the extent of non-adherence and consequently the risk of development of resistant strains through sub-therapeutic levels of medication.

As the rapid expansion of ART began in 2004, laboratory facilities were inadequate to meet the increasing demand for Cluster of Differentiation 4 T-helper Cell (CD4) counts and viral loads. Although many of the sites that were initiating ART in the country had the equipment on site to analyse CD4 count by 2008, major challenges were the erratic supply of reagents and consumables and the downtime of these machines (Ministry of Health and Child Welfare, Zimbabwe 2008b). Equipment for virological monitoring of the HIV disease was not available at state-owned facilities. Measurement of indicators on the progression of HIV disease such as CD4 count and viral load are central to initiation of treatment and the management of patients taking antiretrovirals (ARVs), and can offer an indication of adherence to therapy and its possible outcomes of development of resistance and treatment failure. Although adherence monitoring does not replace the need for virological and immunological monitoring, limited access to these laboratory services increases the need to monitor adherence in striving for desired clinical outcomes among children on ART (Bisson et al. 2008).

By 2008, the health information systems and patient management information systems for ART in Zimbabwe were in their infancy and were mainly paper based. The MoHCW (Ministry of Health and Child Welfare, Zimbabwe 2008b) report on the OI/ART programme highlights challenges in the monitoring and evaluation reporting systems. With the growing number of people on treatment, there were challenges in using this information for management of individual patients. Whilst adherence monitoring was mainly done through pill counts and self-reports, using pill counts as an adherence monitoring method requires well-functioning health information systems and particularly patient management information systems.

The study was planned at the beginning of 2009 when Zimbabwe was facing severe socio-economic challenges. There was evidence of the deterioration of health services resulting from both shortage of health staff and medical supplies (Ministry of Health and Child Welfare, Zimbabwe 2009a, NewsMedical.Net. 2007) as well as concurrent electricity and water shortages in most rural centres and urban municipalities nationwide (NewsMedical.Net. 2007). Fuel shortages had impacted on transport services. Food shortages accompanied by unprecedented inflation rates put intense strain on families who spent much time looking for basic food items and other commodities (de Castella 2003, Skovdal et al. 2011). Players in the provision of ART services were uncertain of the impact of these factors on adherence to

ART, especially among those people coming from the less resourced families. Available evidence indicated that crisis and conflict in Africa have been found to reduce the proportion of HIV positive children returning for care at health facilities, especially amongst the groups that are directly affected (Vreeman et al. 2009, Veenstra et al. 2010), thereby flagging a potential problem with adherence to ART that could worsen.

1.2 Problem statement and motivation for the study

Whilst adherence to ART among children is currently a priority area in HIV treatment programmes (UNAIDS 2010), adherence monitoring, which is a prerequisite to improving adherence through effective interventions, remains a challenge (Nachega, Mills & Schechter 2010). Although adherence levels for the people on ART in Zimbabwe were reported to be high from the programmatic point of view (Ministry of Health and Child Welfare, Zimbabwe 2008a), these were based on routine adherence monitoring methods that included pill-counts and self-reports, the accuracy and feasibility of which had not been assessed in these settings. Among children taking ART, self-reports have been widely reported to exaggerate adherence levels (Farley et al. 2003a, Wang et al. 2008), whereas pill count adherence levels have been reported in other settings to vary widely when compared with those measured using other objective adherence monitoring methods (Farley et al. 2008, Vreeman et al. 2008b). At the time of planning this study there were few validated methods of specifically assessing ART adherence in children (Vreeman et al. 2008b).

From the start of the scale-up of ART in 2004 to the planning of this study in early 2009, no studies had been published on adherence levels to ART among children in Zimbabwe. However, from 2010, a few such studies did appear (Campbell et al. 2012, Ferrand et al. 2010, Mavhu et al. 2013, Skovdal et al. 2011). Non-adherence to medicines had been reported by health staff as a main problem among adolescents on ART in Zimbabwe (Ferrand et al. 2010) and adherence to ART among children and adolescents aged 6-18 years has recently been reported to be suboptimal (Mavhu et al. 2013, Skovdal et al. 2011) although methods used routinely to monitor adherence have not been assessed for accuracy or been validated within these settings.

It was in the context of a developing and expanding ART programme amidst challenges in the health delivery system and a national socio-economic crisis (Mason 2009, Veenstra et al.

2010) that this study was planned. Several concerns around drug resistance and adherence among adolescents and children, as well as a lack of knowledge on the applicability and accuracy of the adherence assessment methods, stimulated the need for research to assess adherence levels among children, evaluate methods of monitoring adherence in these settings and identify factors associated with non-adherence. Consideration of both global and local experience of the challenges associated with adherence monitoring methods revealed a need to identify more accurate adherence monitoring methods that could be applicable for routine monitoring of adherence among children on ART under these conditions.

1.3 Justification for the study

Adherence to ART is essential in suppressing HIV in the blood and in preventing the development of resistant strains that result in treatment failure. Apart from the medical criteria for initiating ART, the potential to adhere to lifelong ART regimens is the major psychosocial criterion for initiating treatment as stipulated in the national guidelines for initiating ART in Zimbabwe (Ministry of Health and Child Welfare, Zimbabwe 2008b, Ministry of Health and Child Welfare, Zimbabwe 2010). Interventions to increase adherence levels and to improve the monitoring of adherence to ART are critical, particularly in children who are already underserved in terms of access to ART (Ministry of Health and Child Welfare, Zimbabwe 2008b).

The need to develop and evaluate clinically useful tools that produce more valid results than current self-report measures for monitoring adherence to ART in resource-constrained settings cannot be overemphasized considering the challenges that are associated with the use of current adherence monitoring methods (Simoni et al. 2006). Despite self-reports being one of the commonly used methods for assessing adherence in clinical settings in southern Africa, a study conducted among a paediatric population on ART in resource-constrained communities in South Africa observed worrying differences between adherence levels measured by self-reports (91% with >95% adherence) and those obtained from Medication Event Monitoring Systems (MEMS[®]) (36% with >95% adherence) (Müller et al. 2008). Studies reporting varying levels of adherence to ART in children in different populations may reflect differences in the sensitivity and specificity of the adherence measuring methods and tools. This has been confirmed in studies that have measured adherence on the same individuals using several methods (Farley et al. 2003a, Müller et al. 2008, Wiener et al.

2004). In general, current clinically applicable methods of monitoring adherence such as the Visual Analogue Scale (VAS), and direct or questionnaire self-report measures have been found to overestimate adherence to medication (Müller et al. 2008). A distinct gap in the literature was identified for research reporting on the development of improved clinically applicable methods for assessing adherence among children in resource-constrained settings, especially in the southern African region.

The design of self-reported adherence monitoring tools should be informed by guidelines on techniques to improve the validity of self-report measures (Gagné, Godin 2005). In two publications, Simoni et al. (2006 & 2007) point out that an ideal adherence monitoring tool should be “reliable, valid and logistically practical with low participant and staff burden” and recommended further research on paediatric adherence to focus on validity and reliability testing of the self-report tools since they are more widely used and are more practical for use in clinical settings. Adherence methods that are considered to be more objective than self-reports have other challenges. Clinic-based pill counts and adherence calendars are subject to possible manipulation by the patients so that they reflect higher adherence levels. Pill counts often result in incomplete data (Farley et al. 2008). Biological markers such as therapeutic drug monitoring, electronic drug monitoring devices, directly observed treatment and unannounced home-based pill counts have complexity, cost and feasibility issues, particularly in resource-constrained settings.

Literature describing factors that influence adherence is replete with conflicting findings, revealing a need to assess adherence in different child populations on ART and a need to investigate challenges to ART adherence in specific child populations, with subsequent adoption of appropriate evidence-based interventions. At the time of planning this study, much of the research on identifying factors associated with adherence to ART in children had been conducted in high-income countries (HIC) (Simoni et al. 2007, Reddington et al. 2000, Mellins et al. 2004). Whilst several studies have been conducted globally on adherence to ART in children, there remains a distinct gap in understanding of factors influencing adherence differences child study populations, adherence monitoring tools and duration over which adherence is monitored (Mannheimer et al. 2008, Simoni et al. 2007). This gap arises from challenges in reconciling conclusions about adherence behaviour and determinants in children from the conflicting findings in the diverse study samples and the range of adherence monitoring tools (Steele, Grauer 2003). There is therefore a need for more research that is of

an appropriately high quality to be included in review articles and meta-analyses and which will provide better insight into adherence to ART in children. Using several adherence measures at the same time to identify factors influencing adherence to ART in the same population is key to explaining the conflicting findings in literature on the nature and influence of certain characteristics on adherence behaviour and hence closing this knowledge gap.

Although recent studies on paediatric adherence to ART have shown an increase in sample size, earlier studies included a sample size of less than 100, with some sample sizes as low as 26. These low numbers possibly reflect the limited availability of ART to children in the earlier years of ART in low- and middle-income countries (LMIC), as well as the limited number of children in HIC infected with HIV who needed ART (Farley et al. 2003a, Reddington et al. 2000, Mellins et al. 2004, Giordano et al. 2004). It is of paramount importance to couple the increased availability of paediatric dosage forms of ARVs and efforts to scale-up ART in children with studies that increase the understanding of adherence to ART in children living in resource-constrained settings. These studies will increase both the understanding of practical methods of monitoring adherence and knowledge on interventions to improve adherence to ART.

1.4 Aim and objectives of the study

1.4.1 Overall aim

To design and conduct an initial evaluation of a new self-reported paediatric adherence monitoring tool, assess the feasibility of using pill count methods in monitoring adherence and identify challenges to treatment adherence and adherence reporting, among children on ART in rural and urban Zimbabwe.

1.4.2 Specific objectives

- Establish levels of adherence to ART in children
- Identify factors associated with non-adherence and challenges to adherence.
- Design and conduct an initial evaluation of a ‘past 10 days’ visually- and verbally-cued self-reported adherence monitoring tool.
- Assess the feasibility of using pill count methods in the study settings.
- Identify barriers to reporting adherence accurately.

1.5 Overview of research design

A dual centre, superiority, parallel design randomized controlled trial (RCT) was conducted for the evaluation of a newly-developed visually- and verbally-cued self-reported adherence monitoring tool for assessment of adherence in children who were receiving ART at two sites in Zimbabwe. Two pill count methods were compared and assessed for their usefulness in routine monitoring of adherence to ART in children in the study settings. Based on a previous study highlighting challenges with the quality of pill count data (Martin et al. 2009), the percent discrepancy in pill counts, a measure that is related to the pill count method, was formulated and assessed as a measure for both adherence and medication-handling behaviour. Factors associated with non-adherence in children were identified using reported adherence, and adherence experiences of children and caregivers as well as experiences in reporting non-adherence at health facilities were identified using the focus group approach. Figure 1.1 shows the conceptual framework on adherence and adherence monitoring that was used to guide this thesis.

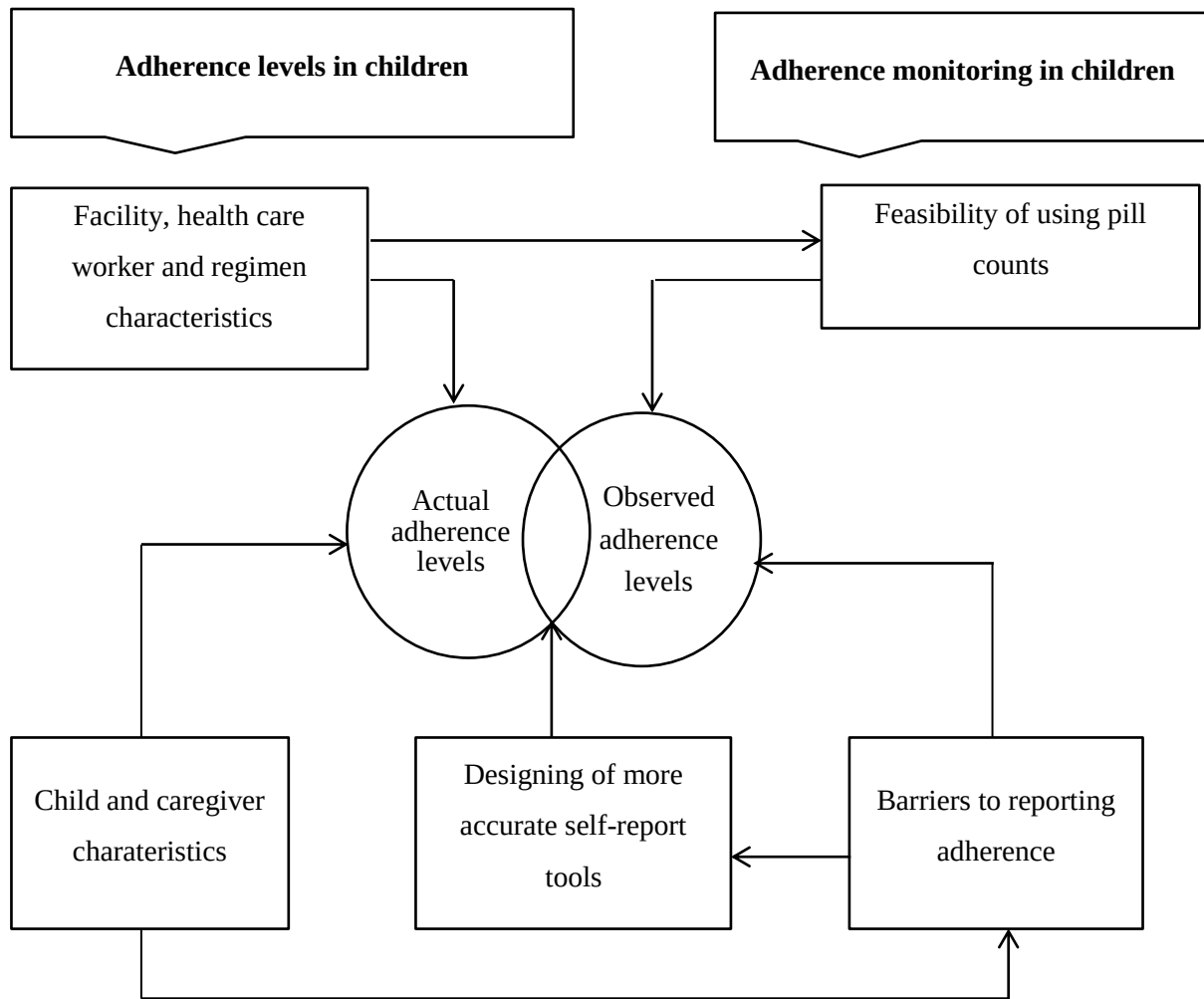


Figure 1.1: Conceptual framework for factors influencing adherence levels and accuracy in adherence monitoring to guide this thesis

1.6 Outline of chapters

Following on from this chapter, three chapters are dedicated to a review of literature that provide the theoretical framework for the thesis and supported the planning and designing of this study. Chapter 2 describes the HIV/AIDS pandemic and ART coverage globally and regionally and summarises international guidelines on prevention of mother-to-child transmission of HIV (PMTCT) and HIV diagnoses and treatment in children. The chapter concludes with a description of the Zimbabwean national ART programme. Chapter 3 introduces adherence to medication and specifically to ART, followed by an in-depth review of adherence to ART in children and factors influencing adherence to ART in this age group in HIC, in LMIC countries, in sub-Saharan Africa and in Southern Africa. At its climax, this chapter presents a critical analysis of adherence monitoring methods and methods used to

validate adherence monitoring tools. Chapter 4 describes the different approaches to conducting randomised controlled trials, explains the application of this method in research and justifies the use of this method in the current study for the validation of a newly-designed self-report tool.

A detailed description of the research methods used in this study is provided in Chapter 5 as well as an explanation of the application and appropriateness of these methods in addressing the objectives of the study. Chapter 6 presents findings from an evaluation of a newly-designed 10-day self-report tool in comparison to an adapted tool from existing internationally used self-report tools, as well as findings from a feasibility assessment of the pill count methods in the study settings. Adherence levels are reported by adherence monitoring methods, adherence thresholds and by the length of the assessment period. Caregiver- and corresponding child-reported adherence levels are compared and factors influencing adherence by these methods are identified. Qualitative findings on child and caregiver experiences with adherence to ART, challenges on adherence and reporting of non-adherence are reported based on information collected from focus group discussions (FGDs) with both children and caregivers.

In Chapter 7, the findings from this study are discussed in the context of international experiences, and more particularly in relation to experiences from other resource-constrained settings. Finally, Chapter 8 concludes the thesis by highlighting the need to assess the feasibility of an adherence assessment method and its possible implications in estimating adherence levels in clinical settings, as is the need for further research that improves the accuracy of adherence monitoring methods that are feasible within resource-constrained settings.

CHAPTER 2: GLOBAL OVERVIEW OF HIV/AIDS AND ART PROGRAMME IN ZIMBABWE

2.1 Overview of the HIV pandemic

The greatest health challenge faced globally over the last two and a half decades has been HIV/AIDS, claiming over 25 million lives (UNAIDS 2010). From 2001 to 2012, the global HIV/AIDS pandemic has been characterized by an increase in the estimated number of people living with HIV from 28.6 million to 35.3 million, and a continuous decrease in the estimated number of new infections from 3.1 million to 2.3 million, amidst an increase in the number of people accessing ART (UNAIDS 2010, UNAIDS 2011, UNAIDS 2013a, UNAIDS 2013b, World Health Organization). Prevention strategies have mainly contributed to a slowing down of HIV infection rates whilst increased access to treatment and care has been partially responsible for the increased number of people living with HIV over the years (UNAIDS 2009, UNAIDS 2013b,). The latter is reflected in the decrease in the estimated number of AIDS-related deaths from 2.1 million in 2004 when the scaling up of ART in the most affected LMIC started, to 1.6 million in 2012 (UNAIDS 2010, UNAIDS 2011, UNAIDS 2013a, UNAIDS 2013b, World Health Organization,).

Sub-Saharan Africa has been most affected by the HIV/AIDS pandemic and, by the end of 2001, an estimated 20.9 million people in this region were living with HIV (UNAIDS 2013a). At the end of 2009, an estimated 22.5 million people were infected with HIV in the region (UNAIDS 2010). Two years later, this figure had increased to 23.5 million people (UNAIDS 2013a). A larger percentage of adults in the region (4.9%) were living with HIV by the end of 2011, compared to a global average adult prevalence of 0.8% (UNAIDS 2013a). Despite the region being one of the two that experienced the sharpest decline in new infections of HIV (25% decline) in the decade up to 2011 (UNAIDS 2013a), 71% and 70% of the global new HIV infections and AIDS-related deaths respectively, occurred in the region in 2011 (UNAIDS 2013a).

Within the region, southern African countries are the most hit by the HIV/AIDS pandemic with all nine countries having the highest HIV prevalence worldwide. Three countries in southern Africa, South Africa, Zambia and Zimbabwe were among the five countries that represented the largest epidemics in the world by the end of 2009 (UNAIDS 2010). At the

end of the same year, the highest adult HIV prevalence in the world (25.9%) was in Swaziland (UNAIDS 2010) and the largest population of people living with HIV (5.6 million) was found in South Africa (World Health Organization, UNAIDS 2011). Although the number of new infections within this region is falling, the southern African region carried approximately a third of the global HIV burden by the end of 2009 (UNAIDS 2010).

Zimbabwe is one of the southern African countries worst affected by HIV and AIDS (UNAIDS 2013a). Within a population of approximately 12 million people, an estimated 1 187 822 million people countrywide were living with HIV by the end of 2009 (Zimbabwe 2010). The country, however, has been reporting a decline in HIV prevalence in the past few years with figures among antenatal women declining from 26% in 2002 to 18% in 2006 (UNAIDS 2007) with further decline to 16.1% in 2009. The annual HIV incidence in the capital, Harare, which reached its peak of 5.5% in 1991, was reported to be at 1% in 2010 (World Health Organization, UNAIDS 2011). This steady decline in the incidence and consequent prevalence of HIV in Zimbabwe was associated with a change in sexual behaviour among its general population (UNAIDS 2009), which in turn appears to have been facilitated by an increased awareness of AIDS deaths and the adverse economic environment experienced in the first decade of the 21st century. The latest 2013 UNAIDS report, however, shows that, lately, there has been an increase in risky behaviour (UNAIDS 2013b).

2.2 The impact of the HIV pandemic on children

The HIV/AIDS pandemic has not only drained the benefits of years of investment in improving the health of children but has caused a drastic increase in the number of orphaned children. Both HIV/AIDS and child health have been streamlined in key global agendas on human development. Millennium Development Goal (MDG) 4 focuses on reducing child mortality, whilst MDG 6 flags HIV/AIDS as one of the major health challenges to be addressed (World Health Organization 2010c).

Worldwide, an estimated 2.5 million children under the age of 15 years were living with HIV by the end of 2009 (UNAIDS 2009, UNAIDS 2010,). Of late, global trends have been showing a decrease in the number of new infections among children. In 2008, an estimated 430 000 children <15 years were newly infected with HIV vertically, with 90% of these being in sub-Saharan Africa (UNAIDS 2009), which reduced to 330 000 in 2011 (UNAIDS

2013a). This decrease is mainly accredited to the impact of programmes, particularly PMTCT.

In Zimbabwe, 152 189 children under the age of 15 years, representing 3.1% of the children in this age group, were living with HIV by the end of 2009 (Zimbabwe 2010). An estimated one million were orphaned by HIV and AIDS at the end of the same year, with 16% of children under the age of 18 years having lost one or two parents (UNAIDS 2010). Children orphaned due to HIV and AIDS are often made vulnerable emotionally, psychologically and economically through the gaps introduced when they lose their first line of support and protection, their parents. Households with orphans have been reported to be grandparent headed, female headed and are poorer than households without orphans (Miller 2010). More orphans than non-orphans live in the streets in Zimbabwe and Zambia (Gillespie, Norman & Finley 2005). In a study conducted in Zimbabwe, close to a third (30%) of school age orphans were found to be out of school (Mangoma, Chimbari & Dhlomo 2009). In most cases these children are not only vulnerable socially and economically but have to struggle with the lifelong condition in the absence of their intimate caregivers, the parents (Vreeman et al. 2008a). Whereas AIDS orphans have a higher risk of having been vertically exposed to HIV from the parents, generally orphans have a higher risk of acquiring infection through horizontal transmission as a result of early sexual encounters and forced or commercial sex (Birdthistle et al. 2008).

2.3 Strategies to reduce vertical transmission of HIV in children

2.3.1 Effectiveness of PMTCT interventions

Vertical transmission from mother to child is the major source of HIV in children accounting for more than 90% of all new infections (Ministry of Health and Child Welfare, Zimbabwe 2009b). Without appropriate intervention, approximately 30% of children born to HIV-infected women become infected with HIV through MTCT. Breastfeeding, the best way of infant feeding, can extend the risk of HIV infection beyond the intra-partum stage (Thior et al. 2006, Coutsoudis et al. 2001). There is a need to intensify efforts to reduce MTCT in the region in the coming two years, if the global goal of zero new infections by 2015 is to be reached (UNAIDS 2013a).

Globally, PMTCT programmes have contributed significantly to a reduction of HIV infection in children. In a comprehensive national surveillance study conducted in the UK, combinations of two interventions that included Highly Active Antiretroviral Therapy (HAART), planned Caesarean section, planned vaginal delivery and zidovudine monotherapy were found to result in MTCT rates below 1.5% (Townsend et al. 2008). A systematic review of studies on PMTCT in LMIC, and particularly in sub-Saharan Africa, revealed that interventions to reduce MTCT are cost-effective in these settings (Johri, Ako-Arrey 2011). Transmission rates below 5% have been reported in Botswana for women taking zidovudine monotherapy during pregnancy and delivery, with or without single dose nevirapine (NVP) (Shapiro et al. 2006). In Zimbabwe, recent intervention options based on 2010 World Health Organisation (WHO) guidelines for PMTCT have been found to have cost-effective advantages over earlier interventions based on women taking a single-dose of NVP (Perez et al. 2012).

Access to effective PMTCT regimens by HIV positive pregnant women has remained low over the years with only 26% of pregnant women in LMIC receiving an HIV test and just above half (53%) of the pregnant women living with HIV receiving ARVs for PMTCT in 2009 (UNAIDS 2010). Latest reports by UNAIDS (UNAIDS 2013b) show only a slight improvement, with 62% of HIV positive pregnant women accessing effective ARV regimens for PMTCT in 2012.

2.3.2 Improved efficacy of PMTCT regimens

In recent years, there have been efforts to improve the efficacy of PMTCT interventions in LMIC by moving away from single dose NVP to more efficacious regimens beyond zidovudine monotherapy (Ministry of Health and Child Welfare, Zimbabwe 2009b, Chasela et al. 2010). The WHO 2010 PMTCT guidelines recommend that all women with a CD4 count below 350 cells/mm³ or those in WHO Clinical Stages 3 and 4 be initiated on treatment for both PMTCT and for their own health, whilst those who are not eligible based on these criteria are given ARV prophylaxis early in pregnancy with the extension of the ARVs to the mother or child during post-partum risk periods (World Health Organization 2010a). Recent developments that are still under consideration by countries include WHO recommendations to put all HIV positive women on triple ARVs for life (World Health Organisation 2012).

2.3.3 Need for ART despite PMTCT

Although proven to be highly effective, strategies to reduce MTCT do not offer 100% protection against the child becoming infected perinatally. There are still those who pass through the safety nets, either through missed opportunities or through lack of effectiveness of the interventions. In 2008, only 36% of HIV positive pregnant women in Zimbabwe were reported to have received ARVs for PMTCT (UNICEF 2009) and in 2009, 21% of the 4208 HIV-exposed babies who were tested by deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) nationwide were found to be positive (Ministry of Health and Child Welfare, Zimbabwe 2009b). The need to avail care and treatment to those children who happen to pass through the safety nets of these prevention programmes cannot be overemphasized, since in the absence of ART, death is expected to occur in 35% of all HIV-infected children by the age of one year and 53% by the age of two years (Newell et al. 2004). HIV-infected infants and children experience a much faster progression of the infection and have much higher viral loads than adults since their immune system is immature (Goulder et al. 2001).

2.4 Overview of ART

2.4.1 Global effort and progress on ART since 2000

There has been a tremendous increase in the number of people taking ART from 300 000 in 2002 to 9.7 million in 2012 (UNAIDS 2011, UNAIDS 2013b, World Health Organization). International steps to fight HIV/AIDS started with the United Nations Millennium Declaration signed in 2000 (Assembly 2000), followed by the 2001 United Nations Special Session on HIV/AIDS (Assembly 2001), and the eight MDGs which articulated specific targets to be achieved by 2015 as derived from this declaration (United Nations, Dept. of Public Information 2005).

The launching of the “3 by 5” strategy in December 2003 by WHO and UNAIDS, jointly, marked the beginning of an era of expanding ART to the general population in LMIC (Gutierrez et al. 2004). Prior to this period ART was widely accessible only to those in HIC, with great improvements in mortality rates of those infected with HIV due to availability of ART (Bhaskaran et al. 2008). The “3 by 5” targets of treating three million people in LMIC by the year 2005 challenged governments, the UN system, foundations and corporations to scale-up ART and build healthcare capacity. In June 2006, at the United Nations General Assembly High-Level Meeting on HIV/AIDS, United Nations Member States agreed to work

towards the goal of “universal access to comprehensive prevention programmes, treatment, care and support” by 2010. Despite failure to meet this target, there has been a rapid expansion of ART programmes globally (UNAIDS 2009). Four million people, representing 42% of all people, and 38% of children in LMIC were on treatment by end of 2008 (UNAIDS 2009), a 10-fold increase in five years. An additional 1.2 million people, representing a 30% increase in the year, were initiated on treatment in the following year bringing the estimated number of people on ART by the end of 2009 to 5.2 million. ART coverage, however, fell short of meeting the target on universal access by 2010 (UNAIDS 2011, World Health Organization). Significant progress has now been made on the UNAIDS target to have 15 million people on ART by 2015 (UNAIDS 2013a). According to the 2012 UNAIDS report (UNAIDS 2013a), 8 million people globally were on ART by the end of 2011 with more than half (54%) of those eligible patients in LMIC taking the life-saving medication. Although the coverage of ART in LMIC had increased to 61% in 2013, according to 2010 WHO guidelines on initiating ART, the coverage in the same year was lowered to 34% of all eligible patients due to the raising of the CD4 threshold for initiating ART under the latest 2013 WHO guidelines (UNAIDS 2013b).

2.4.2 ART coverage in sub-Saharan Africa

Coverage of ART in sub-Saharan Africa increased from about 2% in a five year period to 44% by end of 2008 (UNAIDS 2009). In 2010, WHO released new guidelines for ART which recommended initiation of ART in earlier stages of the HIV disease (World Health Organization 2010b). Based on these new guidelines, ART coverage by the end of 2009 was estimated to be 41%, increasing to 56% by the end of 2011, a figure which, although slightly above the global coverage (UNAIDS 2013a), is still low.

Access to medicines in Africa is a challenge with nearly 80% of the four million people on ART coming from Africa and yet 80% of the medications they are taking come from outside Africa. There is currently a need to increase production of ARV medicines within the African region to reduce their cost and increase access to those who need these lifesaving drugs, taking advantage of the flexibilities provided for in the Trade Related Aspects of Intellectual Property Rights (TRIPS) Agreement. The commitment to increase production of ARVs in Africa is reflected through the Pharmaceutical Manufacturing Plan of Africa (Union 2007). This has already been replicated to the sub-regions, with the Southern African Development Community (SADC) region making an effort to see the implementation of its Pharmaceutical

Business Plan in improving access to medicines (Southern African Development Community (SADC) 2007).

2.4.3 Coverage of ART in children

According to UNAIDS (UNAIDS 2010), global coverage of ART in children (28%) was significantly lower than that for adults (37%) based on the WHO 2010 guidelines for initiating ART and, as reported in the latest UNAIDS 2012 report, the trend has not changed. Despite a general increase in the coverage of ART in the sub-Saharan region, disparities in ART coverage have persisted. By the end of 2011, global coverage of ART in children was only 28% compared to 58% in adults (UNAIDS 2013a). At the end of 2009 when this study was conducted, sub-Saharan Africa was home to 90% of HIV-infected children and yet ART coverage in this age group was only 26%. Amongst countries with high numbers of people living with HIV in the southern Africa region, only South Africa and Botswana reported ART coverage rates in children that were comparable to those in adults whilst Zimbabwe reported an ART coverage rate in children of 30% (UNAIDS 2010).

Difficulties in diagnosing HIV in children, especially very young babies, as well as lack of expertise among health workers in initiating children on ART, have been some of the challenges identified as leading to the low coverage of ART in children in the past (WHO, 2007c; McKellar, Callens, & Colebunders, 2008). Previously, treating younger children required liquid dosage forms and these are far more expensive than the corresponding adult oral solid dosage forms hence limiting their availability. The advent of solid dosage forms that are suitable for administration to the majority of the children who need treatment has contributed to the increase in number of children on ART in the past few years, but ART coverage in children remains lower than in adults.

2.5 Diagnosis and management of HIV in children according to 2006 WHO guidelines

2.5.1 HIV diagnosis in children

Diagnosis and management of children with HIV at the time of the study was guided, through national guidelines, by the 2006 WHO Guidelines on Management of HIV Infection and Antiretroviral Therapy in Infants and Children (World Health Organization 2006b). These guidelines promote early active identification of potential HIV infection in children. HIV diagnosis should be done with antibody tests for children aged 18 months or older and with

virological tests for children younger than 18 months. Care should be taken in virological diagnosis of HIV in children less than six weeks and children who breastfed in the past six weeks since a negative result may test positive at a later stage. Similarly six weeks must lapse after stopping breastfeeding before an HIV negative diagnosis is made for children 18 months or older (World Health Organization 2006b). However, limited resources can limit the diagnosis of HIV in children younger than 18 months resulting in delayed access to treatment and care.

2.5.2 Clinical and immunological staging of HIV disease in children

Classification of HIV disease in children forms the basis of initiating ART. There are two main types of classifications, clinical or immunological. Two immunological criteria are available, CD4 measurements and total lymphocyte count. However because of the age dependency of these immunological markers, the classification is stratified by age. Table 2.1 below provide details on the use of the WHO criteria in the diagnosis of HIV disease and subsequent use of these criteria in initiating ART in children (World Health Organization 2006b).

The CD4 antigen-bearing T-lymphocytes subset (CD4 cells), also known as the T-helper cells, are the primary target for HIV since the CD4 antigen is the primary binding site for HIV, resulting in the progressive loss of these cells that can eventually lead to AIDS. In children, CD4 cells increase from mid-gestation until six months of age before they start declining to adult levels by the age of about six years (Denny et al. 1992, Idigbe et al. 2010, Likanonsakul et al. 1998, World Health Organization 2006b). Apart from being used in clinical diagnosis and initial staging of the HIV disease, CD4 counts can be used to monitor HIV patients together with adherence data and have been found to be as good in predicting current breakthrough viraemia as adherence information (Bisson et al. 2008).

Table 2.1: WHO classification of HIV-associated clinical disease and associated HIV immunodeficiency using CD4 measurements and criteria for initiating ART^a

Classification of HIV-associated immunodeficiency	WHO ^b Clinical stage	Age-related CD4 values			
		≤11 months	12-35 months	36-59 months	≥5 years
Not significant	1	>35%	>30%	>25%	>500 cells/mm ³
Mild	2	30%-35%	25%-30%	20%-25%	350-499 cells/mm ³
Advanced	3	25%-29%	20%-24%	15%-19%	200-349 cells/mm ³
Severe	4	<25%	<20%	<15%	<15% or <200 cells/mm ³
		Age-specific recommendation to initiate ART ^{c, d}			
		<25%	<20%	<15%	<15%
		<1500 cells/mm ³	<750 cells/mm ³	<350 cells/mm ³	<200 cells/mm ³

^aAdapted (World Health Organization 2006b, World Health Organization 2006c).

^bSee WHO guidelines for 2006 as referenced below.

^cART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.

^dCD4% is preferred for children aged <5 years.

2.5.3 Cotrimoxazole prophylaxis

In the 2006 guidelines, WHO (World Health Organization 2006b, World Health Organization 2006a) recommends initiation of cotrimoxazole prophylaxis in HIV-exposed infants starting at 4-6 weeks after birth, for the prevention of *Pneumocystis jiroveci* pneumonia, malaria, bacterial diarrhoeal disease and other pneumonias (World Health Organization 2006b). In children aged 1-5 years, cotrimoxazole prophylaxis should be initiated in children with a CD4% <25% or clinical stages 2, 3 and 4 regardless of clinical staging. Children six years of age or older should be initiated on cotrimoxazole prophylaxis only if CD4 count is below 350 or the WHO clinical staging is stage 3 or stage 4 regardless of CD4 level. In resource-constrained settings the cut-off point for initiation of cotrimoxazole can be lowered to CD4 of 20% in children 1-5 years and CD4 count of 200cells/mm³ in children six years or older (World Health Organization 2006b).

2.6 Recent WHO recommendations on management of HIV in children

2.6.1 WHO 2010 guidelines

In 2010 and 2013, WHO issued new recommendations on ART (World Health Organization 2010b, World Health Organization 2013). Major changes in the 2010 guidelines include earlier and more accurate diagnosis, earlier initiation of ART, simplified regimens, more strategic monitoring of efficacy and toxicity, and strengthened adherence monitoring. Recommendations on earlier diagnosis involve establishing if the child is exposed or not at birth or soon after birth and serological assay testing of the HIV-exposed infants at 4-6 weeks. HIV positive infants should be initiated on treatment upon diagnosis and children 2- <5 years should be initiated on treatment if CD4% is $\leq 25\%$ or CD4 count is ≤ 750 cells/mm³. Those children ≥ 5 years should be initiated on treatment if CD4 count is ≤ 350 cells/mm³. The guidelines promote the use of fixed-dose combinations (FDCs) as these are likely to promote adherence, and the use of protease inhibitors in children who have had prior exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as NVP. In these guidelines, supporting adherence using aids such as pill boxes, calendars and diaries are recommended. The guidelines also highlight problems with existing methods of evaluating and monitoring adherence in resource-constrained settings (World Health Organization 2010b).

2.6.2 WHO 2013 guidelines

The updated guidelines issued by WHO in 2013 further lowers the immunological and clinical threshold of initiating ART. All children <5 years of age should be initiated on ART regardless of clinical or immunological staging and those ≥ 5 years of age should be initiated on ART if they have a CD4 count ≤ 500 cells/mm³, regardless of clinical staging, or if they have HIV disease in WHO clinical stages 3 and 4, regardless of age and CD4 count (World Health Organization 2013).

2.7 Antiretroviral services in Zimbabwe before 2009

2.7.1 The organization of the Zimbabwean health sector

The Zimbabwean health system is composed of four major sectors: state-funded public health institutions, private not-for-profit health institutions including mission hospitals that are run by faith-based organizations, private for-profit health institutions and allopathic practitioners that include traditional and alternative medicines. Health services are organized into health

promotion, disease prevention, diagnosis, treatment and care. Apart from the health facilities, a wide range of groups and organizations contribute to the health delivery system including universities, the pharmaceutical industry, non-governmental organizations and community-based groups.

The public healthcare system is organized into 10 provinces, eight of these being managed by the MoHCW whilst the remaining two are under the municipalities of the two largest cities, Harare and Bulawayo. Public healthcare services are offered at community level, and at primary, secondary and tertiary health facilities. The primary health facilities are mainly composed of central government and local government clinics, secondary health facilities are dominated by central government district hospitals and faith-based mission hospitals, and tertiary health facilities are predominantly provincial hospitals together with the national hospitals that are referred to as the central hospitals, some of which are University Teaching Hospitals.

2.7.2 Antiretroviral treatment programme in Zimbabwe

Until May 2002 when the lack of access to ART was declared as an emergency, the focus of the response to the HIV/AIDS pandemic in Zimbabwe had been primarily to prevent the spread of infection. This state of emergency was extended to 2008. Policy changes emanating from this declaration facilitated importation as well as local manufacture of generic ARVs which are several times cheaper than the corresponding branded products. Previously, these vital medicines were unaffordable to the majority of those in need. As a further commitment to improving access to ARVs, the MoHCW (2004) developed a national plan in accordance with the WHO 'Three Ones' strategy which facilitated identification of possible areas of support by potential partners such as non-governmental organizations, faith-based organizations and foreign donor organizations.

The Zimbabwean government started to provide ART to its population in 2004 (Ministry of Health and Child Welfare, Zimbabwe 2009a). There was a rapid scale-up of sites providing ART services with ART-initiating sites increasing from seven in 2004 to 86 in December 2007. Additional to the ART-initiating sites, ART follow-up sites were established to facilitate quality follow-up services through decentralisation of such services to facilities that are closer to where the beneficiaries live. The rapid expansion of services was facilitated by assessment of health facilities for the provision of ART services and capacity building of

these sites as well as provision of ARVs by the National Pharmaceutical Company of Zimbabwe (NatPharm), a semi-private company. By December 2008 (soon after which this study was planned), there were 107 ART-initiating sites and 175 ART follow-up sites with an approximate 148 144 people on ART countrywide (Ministry of Health and Child Welfare, Zimbabwe 2008b).

Despite these efforts to increase access to ART, the coverage of ART services remained low with only 17% (282 out of 1643) of the health facilities in the country offering ART services in the same year (Ministry of Health and Child Welfare, Zimbabwe 2008b). At the end of 2009, there were 218 589 people on ART and the coverage was 30% in children and 52% in adults based on the 2010 WHO guidelines (UNAIDS 2010). By 2009, inadequate human resources, retention of health staff resulting from the macroeconomic environment, low capacity for processing CD4 counts and clinical tests, inadequate availability of foreign currency for raw materials and purchase of ARVs, as well as geographic inaccessibility of ART sites, high inflation rates and the resulting poverty were major challenges to the provision of ART in the country, (Ministry of Health and Child Welfare, Zimbabwe 2009a, NewsMedical.Net. 2007). Whilst there was an expansion of ART sites and a subsequent increase in the number of people on ART, there was a decline in ART follow-up rates. A low percentage (75.0%) of adults and children were found to be on treatment 12 months after initiating ART as recorded in the Global Fund Round-5 Cohort Analysis Survey in 2009 (Zimbabwe 2010).

Zimbabwe has had three revisions of the national guidelines for ART since the inception of the national ART programmes in 2004. The national guidelines dated May 2010, are based on the WHO 2010 guidelines for ART. The 2010 guidelines raised the threshold of CD4 count for initiating ART in adults from 200/ml to 350/ml, a move that has drastically increased the number of adults in need of ART and consequently lowered coverage of ART in the same population (UNAIDS 2010). Revision of the 2010 national guidelines based on June 2013 WHO guidelines (World Health Organization 2013) which advocate for initiation of therapy in adults and older children with a CD4 count ≤ 500 , is underway.

In the previous WHO 2006 guidelines, initiation of ART in adults and adolescents was based on two main criteria: (i) Medical criteria - WHO clinical stage 3 and 4, patients with peripheral CD4 count of less than 200 and patients with a total lymphocyte count of less than

1200 on two separate occasions; (ii) Psychosocial criteria - demonstration of reliability assessed through adherence to cotrimoxazole prophylaxis medication and keeping appointments as proxies for, and predictors of future adherence with ART, completion of counselling sessions, and lastly availability of and disclosure of HIV status to a treatment partner. In the 2010 national ART guidelines, adherence remained a key consideration before initiating ART and they emphasized the need to make every effort to increase adherence for all on ART (Ministry of Health and Child Welfare, Zimbabwe 2010).

There are several entry points to ART. Patients can be identified through the provider initiated testing approach from the outpatients department and the hospital wards. Other access points include the PMTCT, TB, sexually transmitted infections and family planning units. Patients can be referred from the home-based care programmes and from voluntary counselling and testing (VCT) centres to health facilities providing ART.

2.7.3 Antiretroviral treatment among children in Zimbabwe by 2009

Whilst previous government policies on HIV/AIDS in Zimbabwe did not demonstrate commitment to specifically curb paediatric HIV/AIDS, ART for children and PMTCT have been streamlined in the 2006 to 2010 Zimbabwe National HIV/AIDS Strategic Plans. This commitment is reflected in the separate and distinct reporting of paediatric ART in the National OI/ART Programme 2008 Report (Ministry of Health and Child Welfare, Zimbabwe 2008b).

Like the adult ART programme, the paediatric ART programme has expanded since 2004. In 2007 there were more than 18 major paediatric treatment sites in the country and some of the sites had decentralized ART services to facilitate linkage with the communities (Chima 2007). Despite the efforts to scale-up ART in children, the coverage of paediatric ART in 2008 remained low with 104 sites providing paediatric ART, representing only 6% of the total health facilities in country.

As at the time of planning of this study, in December 2008 there were only four health facilities that were providing HIV virological testing services for early infant diagnosis through dried blood spot testing (Ministry of Health and Child Welfare, Zimbabwe 2008b). The harsh macroeconomic environment presented an additional challenging factor at both programmatic and individual levels. These challenges had the potential to affect adherence to

treatment and subsequent treatment outcomes among the few privileged children on ART (Vreeman et al. 2009).

Paediatric ARVs in the public sector were and are still provided through the government and its collaborating partners. The Clinton Health Access Initiative is one of the major partners that have been providing paediatric ARVs since 2006. Both FDC solid dosage forms and suspensions were being used in the national paediatric ART programme. Approximately 12% of the children were taking ARV suspensions in 2007 and only 1.2% were taking second line regimens (Chima 2007). Increasingly more children started taking FDC solid dosage forms with a bid to move away from liquid dosage forms.

Although the MoHCW (Ministry of Health and Child Welfare, Zimbabwe 2010) released new ART guidelines in 2010 based on the revised WHO guidelines, the period covered by this study was guided by earlier guidelines for the national ART programme. According to these earlier guidelines, the first line regimens included stavudine, lamivudine and NVP. Zidovudine could be used as a first line alternative to stavudine in the event of the latter causing side-effects, and efavirenz could be used in children above the age of 3 years. The recommended second line regimens included zidovudine and didanosine with lopinavir and ritonavir. Child eligibility to receive ART was based on the criteria specified in Table 2.2.

Table 2.2: Criteria for eligibility to receive ART in the Zimbabwe Ministry of Health and Child Welfare Paediatric ART programme^a

Age (months)	Criteria	
<18	HIV exposed or PCR positive result	CD4 count or % based on age OR WHO paediatric clinical stages III and IV
18 or more	HIV antibody positive result	CD4 count or % based on age OR WHO paediatric clinical stages III and IV
<12	1500 CD4 cells/mm ³	25% CD4 cells
12-35	750 CD4 cells/mm ³	20% CD4 cells
36-59	250 CD4 cells/mm ³	15% CD4 cells
≤60	200 CD4 cells/mm ³	15% CD4 cells

^aExtracted (Ministry of Health and Child Welfare, Zimbabwe 2005).

Once the child was found to be eligible for ART based on the above criteria, the child and/or caregiver were counselled on taking ARVs and related issues, and were assessed for treatment readiness. Assessment included access to services, prior adherence to other medications such as cotrimoxazole prophylaxis, availability of a primary care giver and a secondary caregiver where possible, knowledge of the treatment regimen and disclosure of HIV status. Follow-up visits were recommended at two weeks, four weeks and monthly for six months, followed by three monthly follow-up intervals if there were no problems with treatment (Ministry of Health and Child Welfare, Zimbabwe 2005).

2.8 Summary

The greatest health challenge faced in the last two and a half decades has been HIV/AIDS, claiming over 25 million lives globally. Sub-Saharan Africa is the most affected region, having an estimated 22.5 million people infected with HIV in the region in 2009 (UNAIDS 2010). Three countries in southern Africa, South Africa, Zambia and Zimbabwe were among the five countries that represented the largest epidemics in the world by the end of 2009 (UNAIDS 2010). Although Zimbabwe has been experiencing a decline in HIV prevalence, an estimated 1 187 822 million people from a population of approximately 12 million people countrywide were living with HIV by the end of 2009 (Zimbabwe 2010). Moreover, the latest

2013 UNAIDS report shows that, lately, there has been an increase in risky behaviour in Zimbabwe (UNAIDS 2013b).

Worldwide, an estimated 2.5 million children under the age of 15 years were living with HIV by the end of 2009 (UNAIDS 2009, UNAIDS 2010,). Of late, global trends have been showing a decrease in the number of new infections among children (UNAIDS 2013a). This decrease is mainly accredited to the impact of programmes, particularly PMTCT. Somehow, access to effective PMTCT regimens by HIV positive pregnant women has remained low over the years, with only 26% of pregnant women in LMIC receiving an HIV test, and just above half (53%) of the pregnant women living with HIV receiving ARVs for PMTCT in 2009 (UNAIDS 2010). The need to avail care and treatment to those children who happen to pass through the safety nets of these prevention programmes cannot be overemphasized, since in the absence of ART, death is expected to occur in 35% of all HIV-infected children by the age of one year and 53% by the age of two years (Newell et al. 2004).

In Zimbabwe, 152 189 children under the age of 15 years, representing 3.1% of the children in this age group, were living with HIV by the end of 2009 (Zimbabwe 2010). An estimated one million were orphaned by HIV and AIDS at the end of the same year, with 16% of children under the age of 18 years having lost one or two parents (UNAIDS 2010).

There has been a tremendous increase in the number of people taking ART from 300 000 in 2002 to 9.7 million in 2012 (UNAIDS 2011, UNAIDS 2013b, World Health Organization). The launching of the “3 by 5” strategy in December 2003 by WHO and UNAIDS, jointly, marked the beginning of an era of expanding ART to the general population in LMIC (Gutierrez et al. 2004). Although the coverage of ART in LMIC had increased to 61% in 2013, according to 2010 WHO guidelines on initiating ART, this coverage in the same year was lowered to 34% of all eligible patients due to the raising of the CD4 threshold for initiating ART under the latest 2013 WHO guidelines (UNAIDS 2013b).

According to UNAIDS (UNAIDS 2010), global coverage of ART in children (28%) was significantly lower than that for adults (37%) based on the WHO 2010 guidelines for initiating ART and, as reported in the latest UNAIDS 2012 report, the trend has not changed. Difficulties in diagnosing HIV in children, especially very young babies, as well as lack of expertise among health workers in initiating children on ART, have been some of the

challenges identified as leading to the low coverage of ART in children in the past (WHO, 2007c; McKellar, Callens, & Colebunders, 2008).

The Zimbabwean government started to provide ART to its population in 2004 (Ministry of Health and Child Welfare, Zimbabwe 2009a) and at the end of 2009, there were 218 589 people on ART (UNAIDS 2010). Inadequate human resources, retention of health staff resulting from the macroeconomic environment, low capacity for processing CD4 counts and clinical tests, inadequate availability of foreign currency for raw materials and purchase of ARVs, as well as geographic inaccessibility of ART sites, high inflation rates and the resulting poverty were major challenges to the provision of ART in the country, (Ministry of Health and Child Welfare, Zimbabwe 2009a, NewsMedical.Net. 2007). Similarly several challenges were identified in the provision of ART to children in Zimbabwe since 2004 including poor transport and communication networks, late and undersupply of ARVs, inadequate treatment and treatment support facilities, poor and cumbersome record keeping systems, low coverage of ART awareness and education among serviced communities (Chima 2007), poor follow-up of HIV-exposed babies, low utilization of counselling and testing for children, strict eligibility criteria, limited CD4 testing capacity and limited paediatric OI/ART training (Ministry of Health and Child Welfare, Zimbabwe 2008b).

Chapter 3: Adherence to medication

3.1 Introduction

Globally, sub-optimal adherence levels have been reported for prescribed medication in both the HIC and LMIC (World Health Organisation 2003, Banning 2012, Chacko et al. 2012). In 2003, a WHO publication pointed to average adherence levels to chronic medication of about 50% and postulated that this could be lower in LMIC (World Health Organisation 2003). Recent systematic reviews on several health conditions have revealed similar or slightly improved adherence levels in both HIC and LMIC (Chiu et al. 2013, Fidler et al. 2013). However, for some health conditions, adherence levels have been shown to be higher in LMIC than in the HIC (Chacko et al. 2012).

Non-adherence to chronic medication does not only result in deterioration of health but has an economic impact on populations and nations as a result of increased hospitalization (McGrady, Hommel 2013) and mortality, and decreased productivity (van Boven et al. 2013). Whilst there are inconsistencies in the factors that have been identified as influencing adherence, broad categories of factors that have been consistently reported to be associated with adherence include socio-economic-related factors, healthcare team- and system-related factors, condition-related factors, therapy-related factors, and patient-related factors (Kardas, Lewek & Matyjaszczyk 2013).

3.2 Adherence terminology

There has been substantial debate on the use of the three terminologies that refer to the extent to which patients understand and follow the requirements for management of their health conditions, i.e. compliance, concordance and adherence. An analysis of the dictionary meanings of these words shows that compliance is referred to as acting in accordance with or yielding to a desire. There are overlaps in the meanings of the words compliance and concordance, whilst adherence has a slightly different meaning of persistency in a practice or tenet and steady observance or maintenance (Aronson 2007).

The term concordance has been inappropriately used to refer to adherence to medication in some settings (Bell et al. 2007) and its definition has been changing over time (Horne et al.

2005). From the publication of the document advocating for a shift from compliance to concordance by the Royal Pharmaceutical Society of Great Britain (1997), there has been much discussion on the interchangeability of these terms. Some authors have discussed the three terminologies as synonymous (Aronson 2007). Critics have argued that whilst there is a need for a shift away from the compliance approach, mainly because compliance signifies the theoretical intention of prescription, whereas concordance signifies the practical and ethical goal of treatment, (Vermeire et al. 2001) concordance cannot be used interchangeably with compliance or adherence (Bell et al. 2007, Horne 2006). Concordance indicates “the extent to which what the patient thinks about what is asked from him matches what the healthcare-giver thinks the patient actually does” (Vermeire et al. 2001). Bell et al (2007) argues that concordance is not synonymous with either adherence or compliance since the latter two relate to medication-taking behaviour whilst the former does not necessarily refer to this behaviour. He explicitly states that concordance is the interaction between healthcare professional and patient with the aim of establishing a therapeutic alliance hence it is synonymous with patient centred care. In this regard, non-concordance is failure of this interaction resulting in failure to establish this therapeutic alliance.

Although in some cases adherence with health advice is defined as the extent to which one’s behaviour coincides with the advice given (Vik, Maxwell & Hogan 2004), and adherence in relation to medication has been defined as taking the medicine exactly as prescribed, as well as following any other instructions associated with the storage and administration of the medicine or “the extent to which patient follows medical instruction” (World Health Organisation 2003), these definitions have been synonymous with that for compliance. Compliance has been defined as the extent to which the patient’s behaviour matches the prescriber’s recommendations (Horne et al. 2005). Emerging views in the past years have pointed to a deficiency in these definitions since they do not refer to patient involvement in the disease treatment process (World Health Organisation 2003, Horne et al. 2005). This definition has been argued to be insufficient to describe all interventions used in managing the disease. The term instruction has been viewed to refer to the patient as a passive recipient of the issued expert advice rather than as an active collaborator in the management of the disease (World Health Organisation 2003). It is deduced that in this context, non-compliance appears to reflect incompetence or deliberate self-sabotaging behaviour (Horne 2006). For this reason, there has been a shift from the term compliance to adherence. In this regard, the term adherence, which acknowledges that the patient and provider are partners in disease

management and implies patient agreement to the recommendations (Tilson 2004), is distinguished from compliance, in which case the patient is expected to take the expert advice passively without necessarily agreeing to the recommendation (World Health Organisation 2003). Adherence to medication is therefore defined as the extent to which a person's behaviour, taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from healthcare provider (World Health Organisation 2003), or simply, the extent to which the patient's behaviour matches the agreed recommendations from the prescriber (Horne et al. 2005).

Literature has presented a model that includes all three terminologies in which concordance, which has its basis in the health-provider and patient relationship, is an enabling factor to adherence. In this model, adherence incorporates three components: acceptance, which comprises the decision of the patient to agree to take medication, filling in the first prescription and subsequently the first refill, persistence, which is to continue having the refills, and compliance, which is taking the medication at the required frequency and intervals, following any other dietary requirements (Wahl et al. 2005).

Adherence includes taking, as agreed, the correct amount of the medicine each day ('frequency adherence') at the prescribed time intervals ('interval adherence') and following any dietary recommendations while taking the medication ('dietary adherence') (Marhefka et al. 2006b). Complete adherence may be defined as taking 100% of the prescribed doses at the prescribed times and adhering to all other agreed medicine-related instructions. Non-adherence includes anything that is short of this target. However this stringent definition of non-adherence may be of less value in clinical practice as different drugs may require different levels of adherence for a successful clinical outcome. It is therefore desirable to define critical adherence levels when monitoring adherence for a specific treatment (Pullar 1991). Levels of non-adherence can be obtained from the number of doses of a drug or drug regimen missed or taken inappropriately (including incorrect intervals or taken without following dietary indications). Non-adherence levels can also be determined by assessing the number of days when treatment was not taken or the number of prescriptions that were not refilled. Classifying patients as adherent or non-adherent can then be based on the desired levels and nature of adherence for the particular treatment.

3.3 Interventions to improve adherence

Interventions to increase adherence to medications have been implemented for many years in the general patient population (Kripalani, Yao & Haynes 2007) and specifically in children (Fielding, Duff 1999, Graves et al. 2010), for both chronic (Kripalani, Yao & Haynes 2007) and short-term conditions (Haynes et al. 2008). These interventions are numerous (Haynes et al. 2008) and can be grouped into about three categories. Whilst there seems to be wider consensus on the first two groups of interventions which are informational and behavioural interventions (Fielding, Duff 1999, Graves et al. 2010, Kripalani, Yao & Haynes 2007), the third group has been presented as family and social (Kripalani, Yao & Haynes 2007) self-regulatory (Fielding, Duff 1999), or organizational (Graves et al. 2010).

Informational interventions are strategies to educate and motivate patients to adhere and these include face-to-face oral, telephonic, audio-visual or written education, or didactic group classes by a physician, nurse, health educator or pharmacist. Behavioural interventions include reminders in the form of pillboxes, calendars or a change in package, skill building, changes in dosage schedule, reduction in pill burden, tailoring the regimen to the patient's daily routine and rewarding, such as giving feedback on adherence assessment (Kripalani, Yao & Haynes 2007). Self-regulatory skill training involves fostering patients' views of being effective managers of their illness (Fielding, Duff 1999). This may be done by healthcare providers. Family and social interventions include support groups and family counselling (Kripalani, Yao & Haynes 2007). Models of behaviour change such as the Information-Motivation-Behavioral Skills model that has these components have been used to understand and explain ART adherence behaviour (Fisher et al. 2008) and hence support the design of adherence interventions.

A recent review article (Bärnighausen et al. 2011) lists five categories for interventions to improve ART, namely; behavioural, which affect adherence through direct behaviour modification; cognitive, which involves teaching, clarification and instruction; affective, which improves adherence through emotional support; biological, which improves physical ability to take medication; and structural, involving changes in the delivery structure or introducing additional service structures. It is common to combine interventions in these different classes (Bärnighausen et al. 2011, Kripalani, Yao & Haynes 2007) for improved outcomes.

Health conditions that are normally included in adherence interventions are chronic conditions and these include hypertension, psychiatric conditions, asthma, diabetes and AIDS. Adherence intervention studies in short-term conditions are mainly in acute infections (Graves et al. 2010, Haynes et al. 2008).

3.3.1 The effectiveness of adherence interventions

Not all adherence interventions result in improved adherence or treatment outcomes (Kripalani, Yao & Haynes 2007). For adherence interventions to be effective there is a need to establish specific targets for the intervention through identification of what needs to be changed or supported to improve or sustain high levels of adherence (Amico et al. 2013). Ethically, interventions to improve adherence must be judged by how they impact on clinical outcomes (Haynes et al. 2008). Some studies have shown an improvement in adherence following interventions but this improvement was not accompanied with improved clinical outcomes (Kripalani, Yao & Haynes 2007). This finding suggests a possible inaccuracy in the adherence measures, if the increase in adherence was not due to biases in the pre- and post-adherence assessments or the influence of other pharmacological or physiological factors.

The complexity of factors that impact on adherence presents a challenge in establishing universal adherence interventions for all diseases, disease severity, populations and medication type. Effectiveness of interventions may vary by type of disease or by type of intervention (Kripalani, Yao & Haynes 2007). The same intervention was found to be effective for severe asthma attacks but not for mild attacks (Haynes et al. 2008). This phenomenon was also found to apply to interventions aimed at improving adherence to ART. Use of directly observed treatment in enhancing ART outcomes has produced conflicting findings in different studies (Gross et al. 2009, Kaai et al. 2010, Liechty, Bangsberg 2003, Roberts et al. 2004). Those planning adherence interventions may need to consider the frequency and duration of administering the intervention since single interventions might not be effective in maintaining long-term adherence behaviour (Hansudewechakul, Jourdain & Plangraun 2006).

3.4 Evaluating adherence monitoring tools

Although non-adherence is not a clinical condition, non-adherence to medication is a health-related condition that needs to be detected in order to implement interventions that improve adherence and subsequently clinical outcomes. Among other criteria, an ideal adherence monitoring tool must be valid and reliable. Validity refers to how well a tool measures what it is intended to measure or simply the accuracy of a tool or test (Parikh et al. 2008) and reliability refers to the consistency of a measure across different dimensions (Vitolins et al. 2000).

3.4.1 Validity testing of adherence monitoring tools

Four parameters which are used in the validity testing of diagnostic tools are sensitivity, specificity, positive predictive value and negative predictive value (Skaik 2008, Akobeng 2007). Validation of tools using these four parameters provides concurrent validity results against a gold standard. As adherence monitoring tools are similar to and can be classified as diagnostic tools, they can be validated using parameters that are used for diagnostic tools. Sensitivity, specificity, positive predictive value and negative predictive value are also frequently used in adherence monitoring tools to provide concurrent validity results. To be able to use these parameters, there is need for a gold standard, which can be a single test or a combination of tests. The gold standard is the best single test (or a combination of tests) that is considered the current preferred method of diagnosing a particular disease (Parikh et al. 2008).

Additional to these four parameters used to compare measurement tools, it is also common to validate a tool by comparing adherence levels between the experimental tool and a reference tool using correlations (Thompson, Kulkarni & Sergejew 2000), test of mean differences, and test of differences in adherent proportions, or assessing agreement between tools used to rate adherence in the same individual.

Evaluation of adherence monitoring tools, however, is complicated by the lack of a gold standard for monitoring patient adherence, since there is no one measure that has been found to be close to perfect and serve as an ideal standard. MEMS[®], despite having some drawbacks as a gold standard, has been widely used as a criterion reference for this type of validation (Müller et al. 2011). Alternatively biological markers such as viral load, changes in blood pressure (Morisky, Green & Levine 1986) and blood glucose levels have been used as

references for validity testing of adherence in the respective health conditions. In HIV disease, electronic measures (Greenlaw et al. 2010) and virological response are the most commonly used adherence reference standards (Deschamps et al. 2008). Unannounced home-based pill counts (Minzi, Naazneen 2008) and validated self-report tools have also been used as reference standard.

Additional to viral response, changes in CD4 cell count and plasma drug or metabolite levels are considered useful biological markers for use as adherence references in HIV disease. However, even these biological markers have been found to lack 100% specificity when compared with each other (Duong et al. 2001). Biological markers can be used for concurrent validity testing if they are measured concurrently with adherence, or for predictive validation if these are measured at a follow-up period after adherence measurement (Morisky, Green & Levine 1986).

3.4.2 Types of validity

There are three main types of validity; criterion, construct and content validity and within these broad categories of validity are subtypes (Kaplan, Bush & Berry 1976). Concurrent and predictive validity are subtypes of criterion validity. Criterion validity is sometimes referred to as empirical, statistical, (Kaplan, Bush & Berry 1976) or criterion-rated (Vitolins et al. 2000) validity. Convergent validity and discriminant validity provide evidence for construct validity whilst trait validity and factorial validity are synonyms of construct validity (Kaplan, Bush & Berry 1976).

There is controversy as to whether face validity is validity at all. Kaplan, Bush & Berry (1976) argue that face validity is not considered a type of validity whilst Vitolins et al (2000) describe it as a validity type that refers to how acceptable the tool is to the individuals who will rate adherence using it, since failure to accept and/or understand the tool can introduce error into the measurement result.

Content validity refers to the comprehensiveness of the tool in relation to all the elements for the parameter being measured. Construct validity refers to the appropriateness of the selected measures to assess adherence. If the item correlates negatively or positively with another variable in the expected direction and at the expected strength, then it has convergent validity

and if it does not correlate with other variables with which correlation is not expected, then it has discriminant validity.

3.4.3 Calculation of sensitivity, specificity, positive predictive value and negative predictive value

The calculation of sensitivity and specificity is shown in Table 3.1 (Skaik 2008). Sensitivity is the ability of a test to correctly classify an individual as 'diseased' or as having a health condition. This is the probability of being test positive when disease (or health condition) is present. In adherence, this is the probability of being classified as adherent when you are adherent (Müller et al. 2011). This measure is not critical for management of individual health conditions but it is important to health economists since it affects targeting of adherence interventions only to those who need these services.

Table 3.3: Calculation of sensitivity and specificity

	Disease present	Disease absent		
Test positive	a (True positive)	b (False positive)	a + b	PPV ^a [a / (a + b)]
Test negative	c (False negative)	d (True negative)	c + d	NPV ^b [c / (c + d)]
	a+c	b+d		
	Sensitivity [a / (a + c)]	Specificity [d / (b + d)]		

^aPositive predictive value.

^bNegative predictive value.

The ability of a test to correctly classify an individual as disease-free is called the test's specificity. This is the probability of being test negative when disease is absent. In adherence this is the probability of being detected as non-adherent when you are non-adherent and this is critical for individual health management and for management of adherence programmes. If this number is higher (should be close to 100), then it suggests that the experimental tool is doing as well as the gold standard.

Positive predictive value is the percentage of patients with a positive test who actually have the disease (or the health condition). It is the probability of the patient having the disease when the test is positive. In adherence this is the probability of being adherent when you are

classified as adherent. A higher value is in favour of the new tool. Negative predictive value is the percentage of patients with a negative test who do not have the disease and it tells us how many of the test negatives are true negatives. In adherence this is the probability of being non-adherent when one is detected as non-adherent and again this is not critical for individual management but it is important to health economists.

Conventionally the condition (disease) being detected is the undesirable factor whereas when this principle is applied to adherence, the condition (adherence) being measured (or detected) is desirable. Whilst for health condition, the desired outcome is being negative (disease-free), in adherence measurement the desired outcome is being positive (adherent) hence care should be taken and clarification should be done when adopting the terms sensitivity and specificity for use in validating adherence monitoring tools. There are, however, opposing methodologies in classifying positives and negatives when using the above four parameters in validation of adherence tools. Whilst one may approach adherence as the condition of interest (Müller et al. 2011), another researcher may classify non-adherence as the condition of interest (Deschamps et al. 2008), hence when referring to sensitivity and specificity with regard to an adherence assessment tool, it is critical to note whether this relates to non-adherence or adherence. Self-report tools were referred to as having a low sensitivity and high specificity by Deschamps et al (2008) in relation to non-adherence and yet Müller et al. (2011) reported high sensitivity and low specificity of self-reports with regard to adherence behaviour. In the discussion above, sensitivity and specificity were applied to adherence in a manner similar to how Müller et al (2011) apply these terms. This convention will be applied throughout this thesis.

3.4.4 Reliability testing of adherence monitoring tools

Reliability across different times is known as test-retest reliability and that across measurement items is referred to as internal consistency (Thompson, Kulkarni & Sergejew 2000). Internal consistency (Chronbach's alpha) is applied to tools that have several items measuring adherence. Inter-setting reliability is obtained by comparing the performance of a tool across settings. Reliability can also be determined by assessing agreement between two different reporters on the same patient, using the same tool. This type of reliability is known as inter-rater reliability (Thompson, Kulkarni & Sergejew 2000) and the test statistic for this is kappa.

3.5 Methods of assessing adherence to medication

Adherence to medication can be assessed in multiple ways (Berg, Arnsten 2006, Davies et al. 2008, Hecht 1998, Vreeman et al. 2008b), with some methods being simpler, of lower cost and more clinically applicable, whilst others are more suitable for research purposes (Müller et al. 2011). Methods of assessment may be classified as subjective or objective; the main subjective methods are self-reports that include 24-hour, 2-day, 3-day and 7-day recall of adherence up to 365 days, questionnaires, the VAS, and clinician-reported adherence (Butler et al 2004, Nabukeera-Barungi et al. 2007, Shi et al. 2010a, Simoni et al. 2006.). The more objective methods include clinic-based pill counts (Appelgren et al. 2010) or unannounced home-based pill counts (Minzi, Naazneen 2008), pharmacy refill records (Choo et al. 1999), appointment keeping, biological markers such as therapeutic drug monitoring (Mc van Rossum et al. 2002, Back, Gibbons & Khoo 2006) and electronic drug monitoring of which, in the latter case, the most commonly used is the MEMS[®] (Lyimo et al. 2011, Nabukeera-Barungi et al. 2007, Shi et al. 2010a, Shi et al. 2010b). The latter method uses medication caps containing an electronic device that records information when the bottle is opened, with this information then being recorded and read electronically. Adherence support calendars, in addition to being a medication-taking reminder and adherence self-monitoring tool, can be used for assessing adherence at the health facility.

Alternatively, adherence assessment methods may be classified as direct and indirect (Berg, Arnsten 2006). Direct methods involve detection of drugs or drug metabolites (Appelgren et al. 2010) in the plasma or serum. Indirect methods include self-reports, pill counts or syrup measurements, pharmacy refills and electronic monitoring. It is difficult to establish a gold standard for assessing adherence as each method has its own shortcomings (Marcellin et al. 2013). Biological markers are subject to the effects of individual physiological and pathological factors, whilst adherence support calendars, health facility-based pill counts and, to a lesser extent, unannounced home-based pill counts are subject to manipulation by the patient or caregiver (Breton et al. 2007, Müller et al. 2008, Nabukeera-Barungi et al. 2007, Parker et al. 2007). Biological markers such as viral load and changes in CD4 count can be influenced by pharmacokinetic factors and drug resistance that are not associated with non-adherence in the individual and do not accurately reflect non-adherence patterns (Miller, Chang 2002).

Differences in adherence outcomes have been reported with respect to the method used and the specific ways in which adherence is calculated within each method (Müller et al. 2011). There are different methods of calculating adherence, with some studies utilizing mean adherence (Steele et al. 2001) as opposed to proportion adherent and a given cut-off point. The mean adherence among a population provides a general view of adherence in the population whereas proportion of the population that is adherent at a given adherence cut-off point gives a more clinically useful view of adherence levels.

Despite irregularities with all methods of assessing adherence to medication, some methods produce more valid adherence assessment results than others (Müller et al. 2011). In a study conducted in Kenya among children aged 2-18 years on ART, facility-based pill counts revealed significantly higher adherence levels than unannounced home-based pill counts (Nabukeera-Barungi et al. 2007) demonstrating greater possibility of manipulation of amount of remaining medicine by patient or caregiver before visiting health facilities. A study showed that unannounced pill counts were highly correlated with viral loads whilst 3-day recall of adherence was not (Farley et al. 2008). On the contrary, a separate study showed that short-term self-reported adherence over four days was found to be closer to that measured by MEMS[®] than long-term self-reported adherence over four weeks or between health facility visits (Levine et al. 2006), possibly due to the effect of recall bias with long-term recall. MEMS[®] and unannounced home-based pill counts were strongly correlated in psychiatric patients, and in the same study the two objective measures were also strongly correlated but the self-report adherence measures were poorly correlated to MEMS[®] and to unannounced home-based pill counts measures (Velligan et al. 2007).

3.5.1 Biological markers as adherence measures

Biological markers that are used in adherence monitoring include drug or drug metabolite plasma or serum level (Appelgren et al. 2010). Although considered as the most direct measure of adherence, these biological markers have been found not to have 100% specificity against specific biological outcomes. The sensitivity and specificity of protease inhibitor plasma levels to predict virologic response were found to be 90% and 43% respectively with a positive predictive value of 83% and a negative predictive value of 60% (Duong et al. 2001). Drug plasma concentrations were found to have no association with MEMS[®], and unannounced home-based pill counts, self-reports and physician's reports were found to have no association with drug plasma concentrations in psychiatric patients (Velligan et al. 2007).

In HIV disease, virologic response and CD4 count have been found to be associated with adherence and increase in CD4 count was more marked in the adherent group using 4-day caregiver recall (Bhattacharya, Dubey 2011).

Recent evidence alludes to a decreased importance of routine laboratory monitoring of CD4 measurements. Although a study conducted in Zimbabwe and Uganda shows that children and adults who have low CD4 values have remarkably similar and high, mortality risk, similar to untreated cohorts (Walker et al. 2012), there is evidence published by the ARROW trial team (2013) that routine CD4 monitoring was beneficial only after the first year on ART. Moreover during this period the rate of adverse events was low and the team recommended that ART rollout should take priority above routine laboratory monitoring of CD4 cells. This ARROW study conducted in the two countries concludes that the significance of laboratory tests remain in assessment of ART eligibility, to confirm clinical decisions to switch to second-line ART, and for diagnosis and management of intercurrent infections.

3.5.2 Electronic adherence monitoring using MEMS®

MEMS® are the most commonly used electronic adherence monitoring method and criterion reference standard for validation of adherence tools (Shi et al. 2010a). MEMS® have been found to correlate with CD4% and viral load whereas pill counts and child and caregiver reports did not (Martin et al. 2009). Although MEMS® has been used as the gold standard of adherence measures in some instances (Liu et al. 2006), and has been regarded as one of the most objective means of measuring adherence, this method has, in some instances, been shown to overestimate adherence due to mismatches between bottle opening and actual taking of medicine (Denhaerynck et al. 2008). Contrary to this characteristic of MEMS®, this method may also underestimate adherence where there is a tendency of decanting medication (Wendel et al. 2001) especially through the use of pill boxes. Loss of the cap, non-return due to a different caregiver at follow-up and refilling of the MEMS® syrup into another container when travelling have been found to be problematic when assessing adherence using this method in South Africa (Müller et al. 2011).

Another factor impacting on its reliability is that adherence levels using MEMS® vary with the method used to determine adherence levels. There are four different ways of calculating adherence using MEMS®; MEMS® with a 1-hour, 2-hour and 3-hour window of the correct dose time, and using MEMS® to determine the number of days the correct dose was taken.

These have been found to yield varying adherence levels (Martin et al. 2009). Again there were conflicting findings regarding the correlation between adherence levels measured by these different MEMS[®] methods and biological markers (Martin et al. 2009). An additional drawback of electronic drug monitoring is that it has limited use for routine clinical adherence monitoring due to high costs and other feasibility implications. MEMS[®] was found to be 148 times more expensive than a modified Paediatric AIDS Clinical Trials Group (PACTG) tool for routine monitoring of adherence including cost of equipment, and 30 times when considering only health staff times to use the adherence monitoring method (Müller et al. 2011).

3.5.3 Measuring adherence by pill counts

Pill count method is the second most used method of adherence monitoring after self-reports, according to a South African study (Naidoo, Taylor & Jinabhai 2010). Pill counts have been found to produce adherence levels that are lower than that for self-reports but higher than that for MEMS[®] (Martin et al. 2009, Müller et al. 2008). Contrary to this finding, pill counts have also been found to have similar adherence levels to those of MEMS[®] in a study conducted in the USA among children aged 8 to 18 years. The pill count method is considered to be easy to administer and less costly (Martin et al. 2009). However in this same study as well as in others, challenges in using pill counts have been identified, including patients forgetting to bring in remaining pills, keeping pills in another location, and healthcare providers not conducting the pill counts (Appelgren et al. 2010, Martin et al. 2009). Hospital based pill counts have been shown to overestimate adherence, according to a Tanzanian study (Minzi, Naazneen 2008) whilst another study found that pill counts produced adherence levels that were far below those of prescription refills and self-report among an elderly population, an indication of underestimating adherence levels (Grymonpre et al. 1998).

Several methods of pill counts have been described which disclose the ways that were employed to improve the accuracy of pill counts. One of these is to ask patients to bring in all empty, partially full and full medicine containers at the start of the adherence monitoring period and at every visit thereafter (Martin et al. 2009). Pill counts can be conducted at the health facility (hospital-/clinic-based pill counts) or can be done by health personnel visiting the patient's home without prior arrangement (unannounced home-based pill counts). These two methods have been found to produce different outcomes on the same individuals, with the health facility based pill counts yielding higher adherence levels. Despite these efforts,

challenges remain in terms of completeness and accuracy of data used to compute adherence levels by this method (Martin et al. 2009).

The most commonly used method of pill count is given by the formula below (Martin et al. 2009):

$$\text{Pill count adherence} = \frac{\# \text{ of pills dispensed} - \# \text{ number of pills returned}}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100$$

From this formula, it is evident that the pill count method relies heavily on the availability of accurate data on each of the parameters used in this formula. Both accurate clinical records on the quantity dispensed at the last visit and the date of dispensing, as well as the patient returning all remaining pills at each visit, are preconditions for the reliability of this method. In addition, one assumption when using the pill count method is that all pills missing from the container have been ingested. Studies have shown that patients may have a tendency of keeping pills in multiple locations such as a friend or relative's house (Martin et al. 2009). Another major drawback on pill counts is that they offer no insight into important adherence information regarding the timing of the doses. There might be some bias introduced in using this method since adherence levels are calculated only for those who return pill containers. A study conducted by Davies et al (2008) in South Africa revealed that those patients who did not return medication containers or remaining pills at some visits in the year were less likely to be adherent for those months when they brought the pills.

3.5.4 Challenges of measuring adherence by self-reports

Self-reported adherence is the most commonly used of the adherence monitoring methods since it is inexpensive and easy to apply for routine clinical use, especially in resource-constrained settings (Balikuddembe et al. 2012, Berg, Arnsten 2006). In South Africa, a study on methods of monitoring adherence to ART in clinical settings found that self-reports were the most common method followed by pill counts (Naidoo, Taylor & Jinabhai 2010). This adherence measure has been applied across a wide range of health conditions (Shi et al. 2010a). A systematic review of self-reported adherence showed that this measure is often associated with other adherence measures, viral loads and CD4 counts in HIV disease (Simoni et al. 2006). In other health conditions, self-reports were associated with other adherence measures (Shi et al. 2010a). Weak association between self-reports and electronic

monitoring devices have been observed in a review of studies on dermatological treatment (Greenlaw et al. 2010) and in studies on oral antipsychotic medication (Velligan et al. 2007). Only a small percentage (27%) of studies that were reviewed showed a high correlation between self-reports and electronic adherence monitoring devices, most of which were MEMS[®], whilst just below a third (32%) showed no correlation with these devices (Shi et al. 2010a). In colorectal cancer screening, self-reports were found to vary by patient characteristic (Partin et al. 2008).

3.5.4.1 Association of self-reports and virological outcomes

Despite association with both biological and other adherence measures and its wide use (Simoni et al. 2006), reported adherence has been shown to overestimate adherence levels (Minzi, Naazneen 2008). Reported adherence provides useful adherence estimates since resulting ART adherence levels have been found to correlate with HIV-1 RNA viral loads and viral rebound in HIV disease (Chesney et al. 2000, Glass et al. 2008, Simoni et al. 2006). However, in some instances, the correlation between reported adherence and viral response has been found to be very weak. One study conducted on adherence to ART in children in Cote d'Ivoire demonstrated a very weak association between child- or caregiver-reported full adherence and undetectable viral loads, pointing to a high likelihood that reported adherence may not be a valid adherence measure (Elise et al. 2005). Unreliability of reported adherence in predicting virological outcomes has also been echoed by other studies (Ellis et al. 2006, Farley et al. 2008, Wiener et al. 2004,). In a meta-analysis of adherence studies, caregiver-reported adherence was found to have a very small to small magnitude effect on virological outcomes (Kahana et al. 2013).

3.5.4.2 Association of self-reports and other biological markers

Although reported adherence in HIV disease has been found to be associated with CD4 counts and other indirect measures of adherence, fewer studies demonstrated this association than those which showed association between reported adherence and viral loads (Simoni et al. 2006). In the same health condition, the sensitivity and specificity of reported adherence in measuring actual adherence, as measured by drug plasma concentration, were found to be 91.6% and 38.2% respectively, with positive predictive value of 78.4% and a negative predictive value of 65% (Balikuddembe et al. 2012). This implies that for true non-adherence, self-reports are only capable of identifying 38.2% of the cases.

3.5.4.3 Association between self-reports and other adherence monitoring tools

Among adherence monitoring tools, self-report tools have been found to be problematic in overestimating adherence. Apart from varying by patient characteristics, reported adherence has been found to be consistently higher than that measured using objective methods, an indication that there is a tendency to overestimate adherence levels by using these reports (Giordano et al. 2004, Levine et al. 2006, Vriesendorp et al. 2007).

Whilst self-reports have been found to classify almost all adherent patients as adherent (high sensitivity for adherence (Müller et al. 2011) or low sensitivity for non-adherence (Deschamps et al. 2008), they are poor in detecting those who are non-adherent (low specificity for adherence or high specificity for non-adherence), hence classifying a large proportion of non-adherent patients as adherent whilst almost all those who are adherent are classified as such (Deschamps et al. 2008, Müller et al. 2011). In this context, almost all those who are reported to be non-adherent are truly non-adherent, but on the other side, the method overestimates adherence levels (Kouanfack et al. 2008, Simoni et al. 2007). In his study in a resource-constrained setting in South Africa, Müller et al (2011) found all those who reported to be non-adherent as being non-adherent when compared to MEMS[®]-estimated adherence. However there was a high proportion among those reported as adherent, who were non-adherent based on MEMS[®]. In the same study, 73% of children had adherence levels of less than 80% using MEMS[®] and yet adherence was 100% using caregiver VAS reports for all participants, and 92% of caregivers reported 100% adherence in the ‘past 3 days’ using PACTG-style questions. In another study, agreement between reported partial adherence and medication return was very low (Davies et al. 2008).

3.5.4.4 Types of self-report tools and methods of obtaining reported adherence

Reported adherence measures may vary by the items that are used to elicit adherence, the format of the items and the response options provided to the respondent (Simoni et al. 2006). Whilst recall periods vary from the previous day to 365 days, the most commonly used recall period based on studies published up to about 10 years ago was seven days (Simoni et al. 2006). More recent studies on adherence to ART appear to be using the ‘past 3 days’ and ‘past 4 days’ recall periods except when applying the VAS in which case the ‘past 30 days’ is commonly used as the recall periods (Kahana et al. 2013).

There are different types of self-reported questionnaires (Greenlaw et al. 2010, Simoni et al. 2006). The Adult AIDS Clinical Trials Group (AACTG) adherence measurement form and the corresponding paediatric version, the PACTG adherence Modules I and II, have been the most commonly used self-reported tools both in the original form (Shi et al. 2010b) and in an adapted form such as the Self-Reported Adherence (SERAD) questionnaire (Muñoz-Moreno et al. 2007). Other tools that have been used include the Simplified Medication Adherence Questionnaire (SMAQ) (Blanco, Pérez & March 2005, Knobel et al. 2002, Ventura-Cerdá et al. 2005) and the 24-hour Recall Interview (24RI) whose listed advantages include decreased focus on adherence as well as cued recall, hence minimizing social desirability bias and recall bias respectively (Marhefka et al. 2006b). The 24RI involves collection of information through serial telephonic interviews conducted on adherence in the past 24 hours.

Other types of self-reported adherence tools include patient diaries and the VAS (Shi et al. 2010a), which is one of the most popular self-report measures introduced in recent years. The VAS is a linear scale, usually a 100 millimetre line, ranging from 0% to 100% with or without demarcations at every 10% interval (Welsh, Gettinby & Nolan 1993). Individuals mark a point to indicate the proportion of their prescribed medication they have taken. Self-reported adherence using VAS still presented the challenges of grossly overestimating adherence when compared to MEMS[®] (Müller et al. 2008) and was found to be comparable to other self-report measures (Amico et al. 2006). Even with all these self-report measures, there remains minimal sensitivity of existing self-report measures in their ability to detect non-adherence (Grosset et al. 2006).

Self-report questionnaires such as the Morisky-8-Item Medication Adherence Scale (MMAS-8), Adherence Self-Report Questionnaire (ASRQ), admitted non-adherence instrument, Medication Adherence Self-Report Inventory (MASRI) and risk of non-adherence instrument measure adherence whilst others such as the Morisky-4 scale and the Brief Medication Questionnaire (BMQ) measure reasons for non-adherence in addition to adherence (Greenlaw et al. 2010). Self-report questionnaires ask the frequency of missed doses or focus on the proportions of doses taken (Rasbach et al. 2013).

Self-reports are often elicited during telephonic or in-person interviews or through written (paper or computer-based) questionnaires, with different modes of communication being used in a bid to increase their validity. Self-reported adherence collected through telephonic

interviews were found to be better correlated to electronic drug monitoring than self-reported adherence collected through in-person interviews (Pearson et al. 2007). Another tool using a different mode of self-reporting in measuring adherence is the Computer Assisted Self Interview (CASI) which may have the questions in an audio rather than a written form (Bangsberg et al. 2002).

Versions of the self-reported adherence measuring tool vary in terms of the number and type of questions asked in assessing adherence, from a single-item measure asking how many doses of the prescribed medication were not swallowed in a specified time period, to a set of questions assessing not only 'frequency adherence' but also 'interval' and 'dietary adherence'. The questions range from simple open-ended questions such as, "How many tablets did you miss yesterday?", to a collection of both closed-ended and open-ended questions (Muñoz-Moreno et al. 2007) and in some instances questions involve the use of the Likert scale (Simoni et al. 2006).

The use of these validated tools can be useful in giving estimates of non-adherence along with reasons for this behaviour, as well as for initial validation of new adherence monitoring tools where more objective adherence measuring tools such as MEMS[®] are not feasible or not affordable.

3.5.4.5 Designing and improving the accuracy of self-report tools

Garfield et al (2011), in their review article on self-reports, indicated that a good self-report measure must be brief, acceptable to patients, valid, reliable and able to distinguish between intentional and unintentional non-adherence. The low sensitivity of self- and caregiver-reported adherence measures in detecting non-adherence is ascribed to this type of measure as being subject to social desirability and recall biases (Gagné, Godin 2005). Contributing to the complexity in the accuracy of this measure of adherence, both self-and caregiver-reported and physician-reported adherence to medication may be influenced by clinical outcomes, with patients who have better clinical outcomes having high reported adherence levels that do not concur with the actual medication-taking (Velligan et al. 2007).

A variety of methodologies have been employed in developing self-report tools. Self-report tools can be developed using literature review, input from patients or input from healthcare

professionals. Alternatively a combination of two or all of these methods can be used (Garfield et al. 2011).

Four techniques for stimulating recall in self-reports have been identified; correct wording of questions, using longer questions, using aided recall tools, and specifying a reference time period (Gagné, Godin 2005). Several techniques have been identified for reducing social desirability bias. These include assuring confidentiality, writing questions in a non-threatening way, embedding required questions among other non-threatening questions, reducing the interviewer's role, presenting the perceived undesirable behaviour as a common behaviour ('loading') with the assurance that there is no right or wrong answer, and ensuring patients that they will not be penalized for giving any of the possible responses (Gagné, Godin 2005).

Other methods of improving the accuracy of self-report tools are to combine adherence results from different methods. A study that analysed adherence by both child and caregiver reports showed that the magnitude effect of combined child/caregiver reports on virological outcomes was found to be better than those for caregiver alone (Kahana et al. 2013).

3.5.4.6 Validation of self-report tools

Self-report tools have been validated using a variety of reference standards including electronic monitoring and virological outcomes (Deschamps et al. 2008, Godin, Gagné & Naccache 2003). Most self-report tools have data on validation but fewer studies report on the reliability of these tools (Garfield et al. 2011). Since there is no ideal adherence measure, several measures, including self-reports, have been used as the criterion standard for evaluating self-report measures (World Health Organisation 2003, Greenlaw et al. 2010) including self-report tools such as the Morisky-4 scale and its adaptations (Greenlaw et al. 2010). Several self-reported adherence tools have been evaluated in a variety of health conditions such as using blood pressure to estimate levels of adherence to antihypertensive medication, asthma morbidity for asthma medication, MEMS[®] and other previously validated self-report measures, as criterion standards (Greenlaw et al. 2010). Studies show that MEMS[®] (Greenlaw et al. 2010), drug plasma concentrations (Balikuddembe et al. 2012) and viral load in HIV disease (Godin, Gagné & Naccache 2003) have mainly been used in sensitivity and specificity testing of self-report tools, whilst the rest of the tools are only used for correlational analysis or other analyses that involve only the test of association.

3.5.5 Combining adherence monitoring methods to improve adherence estimates

Composite measures of different adherence monitoring tools have been developed in an effort to improve the validity of adherence measures, with conflicting outcomes results. A composite measure of the VAS, returned medicines and PACTG-style 3-day recall was found not to have validity advantages over single measures in a study conducted among children on ART in resource-constrained settings of South Africa (Müller et al. 2011). Contrary to this finding, a different study found that the magnitude of effect of combined child/caregiver reports on these outcomes were better than those for caregiver alone (Kahana et al. 2013).

3.6 Adherence to ART

Antiretroviral therapy involves far more than merely making drugs available to those in need of this treatment. Adherence monitoring, counselling and support are critical in any ART programme as is laboratory support and counselling on healthful living. Non-adherence to treatment has been identified as the main reason for treatment failure (Bangsberg et al. 2001). Other reasons for treatment failure include under-dosing (Menson et al. 2006) resulting from failure to increase dose when the child is growing, post-licensing changes, limitations of certain formulations, poor quality medicines due to poor formulations and deterioration in the quality resulting from poor storage. Treatment failure can also result from drug interactions such as those that occur between rifampicin and NVP, malabsorption when there is chronic diarrhoea, infection with resistant strains and regimens that have low efficacy.

Viral loads below detectable rates were found to be closely related to adherence levels in children on ART (Elise et al. 2005, Farley et al. 2003a) and in general, lower viral loads and virological response were associated with higher adherence levels (Giordano et al. 2004, Oyugi et al. 2004, Van Dyke et al. 2002,) with adherence being shown to predict long-term virological suppression (Bisson et al. 2008, Ford et al. 2010). Adherence is also of importance in minimizing drug resistance which is not only costly to the individual on treatment but to the treatment programmes on a larger scale (Shekelle et al. 2007).

3.6.1 Importance of accurately measuring adherence in ART

Adherence measurement is needed for clinical, public health and research purposes (Berg, Arnsten 2006). Clinicians need to estimate adherence using practical methods that are

efficient and inexpensive when they manage each individual on ART to prevent sub-optimal drug levels and the subsequent development of treatment failure and emergence of resistance. Public health specialists require less costly but accurate adherence assessment methods to obtain close estimates of adherence levels in order to identify target patient populations prior to instituting wide scale interventions to improve adherence (Berg, Arnsten 2006). In research, adherence assessment is needed in clinical trials of drug development, adherence intervention studies, evaluating adherence monitoring tools, estimating adherence levels and identifying determinants of adherence behaviour. When adherence is not accurately measured in these circumstances, incorrect conclusions can be made resulting in a vicious cycle of inappropriate public health action, harmful or inappropriate clinical decisions and inappropriate follow-up research.

3.6.2 Critical adherence levels for ART

In adults, levels of adherence to protease inhibitors of 95% calculated using MEMS[®] and based on the proportion of the prescribed doses that are actually taken, were found to be optimal for virological outcomes (Paterson et al. 2000). Taking <95% of doses by pill count was associated with failure to maintain viral loads below 400 copies/ml among Thai children (Hansudewechakul, Jourdain & Plangraun 2006). Adherence thresholds of 100%, >95%, >90% and >80% have been used in studies that involved monitoring of adherence to ART (Mills et al. 2006).

Adherence levels below 95% may still be adequate for patients on NNRTI but are not adequate for virological suppression in patients receiving partially suppressive unboosted protease inhibitors (Bangsberg 2006). Mean adherence levels of about 70% - 72% may be sufficient for virological suppression in patients taking boosted protease inhibitor regimens whereas those on non-boosted protease inhibitor regimens and NNRTI regimens require far higher adherence levels for the same effect (Pham 2009).

Different methods have been used to measure the association between adherence and virological outcomes at various times after initiating ART in children and this complicates the determination of critical adherence levels. The variations between the methods of measuring adherence, the indicators for measuring response to treatment and the time between the initiation of ART and measuring the impact of treatment, all make it difficult to establish critical ART adherence levels in children (Giordano et al. 2004, Oyugi et al. 2004,

Van Dyke et al. 2002). However MEMS[®] adherence levels of above 80% were associated with viral loads below the threshold of detection six months after treatment, but this does not imply that higher adherence levels cannot achieve better virological outcomes (Farley et al. 2003a).

3.6.3 Adherence to ART globally and in LMIC

Although adherence to ART has been seen to vary widely from study to study, 62% of the people on ART were found to be $\geq 90\%$ adherent in a review of articles worldwide (Ortego et al. 2011). Among HIV positive pregnant women on ART from high, HIC and LMIC, the pooled proportion of women with adequate adherence levels was 73.5% and was higher during antepartum (75.7%) than during postpartum (53.0%) (Nachega et al. 2012). Slightly higher adherence levels were reported in conflict-affected and forcibly-displaced populations in studies identified for a review in both LMIC and HIC, with 87% - 99.5% achieving optimal ($\geq 95\%$) adherence levels (Mendelsohn et al. 2012). Challenges to ART adherence have been identified in both the HIC and LMIC countries (Mills et al. 2006) and in special groups worldwide (Arnsten et al. 2002, Nachega et al. 2012).

Adherence measured mainly by self-reports was found to be higher in sub-Saharan Africa than North America (Mills et al. 2006). It is possible that the observed differences are due to some distinct characteristics in the population which enhances adherence (Ware et al. 2009), or may be due to differences in how populations report on adherence behaviour since recall and social desirability biases are likely to influence this process. Pooled analysis of eight studies in India showed ART adherence levels of 70% (Mhaskar et al. 2013). In Botswana, mean adherence levels by self-reports were very high (98%) and ranged from 70% - 100% (Vriesendorp et al. 2007). High adherence levels may be achieved by the majority of patients at a visit, but challenges in maintaining optimal adherence levels at every visit have been reported in a study conducted in Uganda and Zimbabwe, with less than half of patients maintain optimal adherence throughout the year yet 94% had optimal adherence level at one visit in the year (Muyingo et al. 2008).

3.6.4 Levels of adherence to ART among children

Although comparisons of adherence levels between different settings are conducted (Vreeman et al. 2008b), these comparisons are complicated by the different ways in which adherence levels have been measured and reported. Three review articles on adherence to

paediatric ART have shown that globally, adherence levels range from 20%-100% (Simoni et al. 2007, Steele, Grauer 2003, Vreeman et al. 2008b) but these vary widely in the adherence assessment method, the age of the children, source of adherence information, cut-off points for adherence and whether mean adherence or dichotomised adherence is used. A review article on sub-Saharan Africa studies conducted in Uganda and South Africa reported >95% adherence levels among 72% of study participants using unannounced home-based pill counts and among 36% using MEMS[®], respectively, with high adherence levels (94% taking more than 95% of prescribed doses) by clinic-based pill counts (Müller et al. 2008, Nabukeera-Barungi et al. 2007). A study in Malawi measured adherence over a period of six months among children by caregiver reports of doses missed in the past three days prior to monthly visits and reported adherence in terms of percent children reporting 100% adherence in the past three days (Day 1 to Day 3) periods over six months. Information on the percentage of children who missed doses at each visit cannot be extracted from this report for easy comparison with other past three day adherence levels in other settings. Table 3.2 below shows adherence levels for children reported in three review articles (Kahana et al. 2013, Simoni et al. 2007, Sutcliffe et al. 2008) and in some recent publications on ART adherence in children below the age of 19 years in sub-Saharan Africa (Bagenda et al. 2011, Davies et al. 2008, Haberer et al. 2011, Haberer et al. 2012, Iroha et al. 2010, Polisset et al. 2009, van Griensven et al. 2008, Vreeman et al. 2009, Weigel et al. 2009) and in HIC (Farley et al. 2008, Martin et al. 2009, Steele et al. 2001).

Table 3.4: Ranges of adherence levels among children below 19 years by adherence monitoring method and region

Region	Caregiver reports	Child reports	Clinic-based counts	pill counts	Unannounced home-based pill counts	EDM ^a	Other methods ^b
HIC ^c	34-100	20-97	69-90			25-81	21-100
sSA ^d	27-100	27-98	69-100		39-94	36-95	49-95

^aElectronic drug monitoring.

^bClinic attendance, therapeutic drug monitoring, care provider reports, pharmacy refill.

^cHigh-income countries.

^dSub-Saharan Africa.

A wide range of adherence levels have been reported both in the HIC and LMIC. In a study conducted in Abidjan, Côte d'Ivoire, 33% of children on ART reported less than full

adherence in the month prior to a review date (Elise et al. 2005). A study from the United States found that 42% of perinatally-infected children on ART had adherence levels below 80% using MEMS[®]. Child adherence levels to ART measured by self-reports from adult caregivers of children aged 3-13 years, or from the children themselves if they were seven years or older, were found to be 40% and 56%, respectively (Mellins et al. 2004).

In other studies, full adherence to ART by children was reported in 70% and 57% of children on ART in the previous three and seven days, respectively, prior to the interviews (Reddington et al. 2000, Van Dyke et al. 2002). Some studies have reported adherence levels of between 40% to 75% using different methods which measured adherence over varying periods of time (Elise et al 2005, Farley et al. 2003a, Mellins et al. 2004, Reddington et al. 2000, Van Dyke et al. 2002, Wachholz, Ferreira 2007). These studies demonstrate that adherence to paediatric ART is a challenge both in the HIC and LMIC.

More recent publications on adherence to ART in children have shown higher adherence levels, especially when measured by self-reports. A review article showed that adherence levels among children on ART range between 49% and 100%, with just over three quarters of the studies reviewed reporting adherence levels above 75% (Vreeman et al. 2008b). In some instances self-reports have yielded unbelievably high adherence levels among 84% of the children on ART for perfect adherence (taking 100% of prescribed doses) (Williams et al. 2006) and 91% for excellent adherence (taking more than 95% of prescribed doses) (Müller et al. 2008), contrary to adherence levels obtained through other methods used on the same subjects at the same time. In Thailand, 90% were more than 95% adherent in the first 6 months and 87% were more than 95% adherent in the following six months by pill count (Hansudewechakul, Jourdain & Plangraun 2006). In the USA, children aged 8-18 years were found to have adherence levels of 78% by MEMS[®] 86% by pill counts, 98% by child-report and 99% by caregiver-report over the past three days (Martin et al. 2009). Despite high adherence levels yielded by self-reports, challenges of maintaining optimal adherence levels over time cannot be dismissed. Determination of the extent of non-adherence among children on ART is further complicated by the challenges of questionable accuracy of adherence monitoring methods.

High adherence levels were reported for children 1-14 years in rural and urban Kenya with 98% perfect adherence over the past 7 days being reported by caregivers. However in another

study in Western Kenya, about 73% of children 0-14 years had reports of perfect adherence (Vreeman et al. 2008a). In South Africa, 89% reported >95% adherence in the previous month (Reddi et al. 2007). In Italy, 79% of caregivers reported >95% adherence in the past four days (Albano et al. 2007).

3.6.5 Factors influencing adherence to ART in children

In addition to challenges in scaling-up treatment in children, monitoring and supporting adherence to lifelong treatment in children under the support and responsibility of a caregiver presents complex behaviours, interactions and outcomes to evaluate. Diverse factors have been found to influence adherence to ART among children; these include medication and disease-related factors, the healthcare delivery system, child and caregiver-related factors as well as psychosocial and socio-economic factors.

Administering liquid dosage forms over an extended period of time to a young child who is unable to swallow tablets presents several difficulties. Liquid dosage forms require accurate measurement of the dose using an appropriate measure. The liquid can easily spill or become contaminated during administration, and the unpleasant taste of some liquid dosage forms often results in the child refusing to take the medicine (Reddington et al. 2000, Van Dyke et al. 2002). In recent years solid dosage forms that are suitable to administer to children have been formulated. The type of ARV has been found to influence adherence (Marhefka et al. 2006b) and in another study, those taking efavirenz were found to be more non-adherent than those on first line regimens without efavirenz (Elise et al. 2005). Difficulties in taking nelfinavir and ritonavir were reported although adherence did not differ much between these and other drugs (Van Dyke et al. 2002). Pill burden and side-effects have been pointed out as reasons for non-adherence (Steele, Grauer 2003).

Adherence to ART was found to be higher in children who had been hospitalized twice or more before starting HAART (Nabukeera-Barungi et al. 2007), those with a shorter duration on HAART (Marhefka et al. 2006a), those who had experienced previous adherence assessments and those on antipsychotic medication (Williams et al. 2006).

Child- and caregiver-related factors found to be associated with higher adherence levels included high caregiver educational level (Wachholz, Ferreira 2007, Williams et al. 2006), the caregiver being other than biological parent (Marhefka et al. 2006a, Williams et al. 2006),

greater caregiver regimen knowledge (Martin et al. 2007, Wachholz, Ferreira 2007), using a buddy system to remember medication-taking (Williams et al. 2006), lower caregiver income level, non-disclosure of HIV status to the child and less caregiver psychiatric distress (Marhefka et al. 2006a). Housing instability (Steele, Grauer 2003), older age of the child (Steele, Grauer 2003, Williams et al. 2006), female gender, a recent stressful life event, repeating a grade in school, diagnosis of depression or anxiety (Williams et al. 2006), and the caregiver being the only one who knows about child's HIV status (Nabukeera-Barungi et al. 2007) were all associated with poor adherence. However, conflicting information has been presented on factors affecting adherence to ART in children with regard to age (Elise et al. 2005, Giacommet et al. 2003, Gibb et al. 2003), sex (Williams et al. 2006, World Health Organisation 2003) nature of caregiver (Marhefka et al. 2006a) and knowledge (Martin et al. 2007, Martin et al. 2009, Wachholz, Ferreira 2007). Adherence to ART was found to be lower in children who had a poorer quality of communication with their parents and in children whose caregiver experienced higher stress, lower quality of life and worse cognitive functioning. A lower degree of disclosure to others was significantly associated with non-adherence (Mellins et al. 2004). Children being looked after by caregivers worried about the child's teachers and friends finding out the child's HIV status were found to have missed more doses in the previous one week (Reddington et al. 2000). Caregivers' perceptions on the ease of achieving high adherence levels were also found to be associated with adherence to ART (Reddington et al. 2000). Busy lifestyles for the caregiver or the child may result in the child missing doses especially with medication that has more frequent dosing intervals (Reddington et al. 2000, Van Dyke et al. 2002). Forgetting and scheduling problems have been listed as reasons for non-adherence (Steele, Grauer 2003). These findings point to the importance of family dynamics, caregiver personality, quality of life and lifestyles in influencing the child's adherence levels to ART.

Challenges in the health delivery system can also affect adherence. Effective drug management systems ought to be in place to ensure that ARVs are available at the health facilities at all times. Non-availability of medicines at health facilities has been reported as a non-behavioural cause for non-adherence (Elise et al. 2005).

3.7 Theoretical models and adherence behaviour

Theoretical models of health behaviour change originate from several perspectives which have been classified as biomedical, behavioural (learning), communication, cognitive, self-regulatory and stage perspectives (Munro et al. 2007). The biomedical perspective views patients as passive recipients of doctors' instructions with health and diseases having a biomedical origin and treatment focusing on the human physical body. Based on this view of health and illness, solutions to health problems are therefore of a mechanical nature such as prescribing medication (Munro et al. 2007). Solutions to medication non-adherence are also technological, including interventions such as MEMS[®], calendars and pill boxes to enhance adherence (Kalichman et al. 2005, Munro et al. 2007). The major drawback of this perspective, despite the fact that biomedically-based interventions have been shown to effectively support adherence (Kalichman et al. 2005), is that it does not incorporate factors such as patients' perspectives of benefits and barriers to executing certain behaviours, psychosocial influences and the impact of the socio-economic environment (Munro et al. 2007).

The behavioural (learning) theory concerns the environment and the teaching of skills to manage adherence (Munro et al. 2007). These aspects have been targeted for intervention mostly by healthcare providers providing either one-on-one or group counselling (Kripalani, Yao & Haynes 2007, Simoni et al. 2006). Antecedents, which can be thoughts (internal) or environmental cues (external), and consequences such as rewards (van der Plas et al. 2013) or punishments for behaviour are considered to be key determinants of health behaviour. This perspective, is, however, limited in that it only focusses on external influences, lacks an individualistic approach to behaviour change and does not incorporate influences on behaviour that are less conscious than those stated above (Munro et al. 2007). Studies have shown conflicting information regarding the effectiveness of environmental cues, such as patient reminders, in promoting adherence (Mannheimer et al. 2006, Munro et al. 2007, Simoni et al. 2006).

The communication perspective focusses on the patient-healthcare provider relationship with interventions targeted at improving communication between patient and health practitioners. Patient-provider relationships measured through patient report of satisfaction with care were found to be associated with adherence behaviour in ART (Russell, Krantz & Neville 2004).

In another study, better physician-patient relationships were associated with adherence to ART (Beach, Keruly & Moore 2006, Schneider et al. 2004). Patients who are more satisfied with the care they receive are more adherent, pointing to the importance of the patient-provider relationship in influencing adherence behaviour (Liu et al. 2006, Russell, Krantz & Neville 2004).

Social cognition models are linked by the theory that attitudes and beliefs are major determinants of behaviour. A common approach in these models is that of expectancy value, whereby health behaviour arises from firstly expectancies or beliefs that taking specific actions will lead to certain outcomes, and secondly from the subjective value placed on these outcomes (Horne, Weinman 1999). Theoretical frameworks related to cognitive perspectives include the health belief model (Rosenstock 1966), social cognitive theory (Bandura 1989), the theory of reasoned action (Fishbein, Ajzen 1975), the theory of planned behaviour (Fishbein, Ajzen 1975) and the protection motivation theory (Rogers 1975).

In understanding the psychology of adherence, the theoretical models that have been used as aids are mostly from only three of these categories, social cognition models such as the health belief model (Becker et al. 1978, Rosenstock 1966), stage models, mainly the transtheoretical model (Johnson et al. 2006a) and Leventhal's self-regulatory theory (Leventhal, Diefenbach & Leventhal 1992) that falls within the self-regulatory perspective (Horne, Weinman 1999, Munro et al. 2007).

The health belief model has been specifically developed for use in health behaviour whereas others such as the theory of planned behaviour and the theory of reasoned action have been derived from general models of behaviour and adapted for use in health behaviour (Horne, Weinman 1999). Components of the health belief model have been used in adherence to medication (Becker et al. 1978, Cerkoney, Hart 1980) and in adherence to ART in children (Steele et al. 2001).

3.7.1 Relationship between constructs of theoretical models and adherence behaviour

Whilst a whole model can be used and assessed for its association with adherence (Kelly, Mamon & Scott 1987) certain cognitive variables within constructs of the theoretical models of behaviour change, mainly in the cognitive perspective, have been found to be highly associated with non-adherence (Becker et al. 1978, Horne, Weinman & Hankins 1999).

Several constructs from different models have also been merged to provide a more comprehensive framework of factors that influence specific adherence behaviour (McDonnell, Turner & Weaver 2001). These constructs are pre-determinants of non-adherence behaviour and results from their measurement have been used as proxies for non-adherence behaviour based on the nature of the association between the two measures. The following section will focus on components that have been used explicitly in this study to examine their association with self-reported adherence behaviour based on past research in adherence to ART.

3.7.1.1 Self-efficacy

Self-efficacy is a major determinant of behaviour and has been shown to be associated with medication adherence behaviour (Gatti et al. 2009, Wolf et al. 2007). This construct is part of the social cognitive theory (Munro et al. 2007) and is defined as “a person’s feelings and thoughts about his/her capability of accomplishing any given task” (Buchmann 1997). Medication adherence self-efficacy is one’s confidence in his/her ability to adhere to a medication regimen in the face of challenges (Johnson et al. 2006b). Self-efficacy for a specific behaviour is not a personality trait and it can be learned and enhanced. It is more “context and task specific to a particular behavioural outcome” (McCann, Clark & Lu 2008). Interventions can be designed that enhance self-efficacy through empowerment alongside improving knowledge and coping skills. These interventions can be expected to result in behaviour change that improves the health of individuals. A self-efficacy expectancy scale was validated among caregivers of children on ART and was shown to be both valid and reliable and was associated with adherence behaviour and CD4 cell measurements.

3.7.1.2 Beliefs about medicines

Beliefs about medicines are associated with adherence behaviour, with negative beliefs having been found to be strong predictors of non-adherence behaviour (Gatti et al. 2009, Horne, Weinman & Hankins 1999). Not believing in the importance of adherence was associated with worse adherence and worse patient-provider relationships (Schneider et al. 2004). The health belief model refers to perceived barriers to adherence, which can be factors perceived as a hindrance to taking medication as agreed with the healthcare providers.

In a study conducted in the USA on adherence to ART in children, Steele et al (2001) did not find an association between caregiver perceived vulnerability and perceived benefits with

adherence. Contrary to this finding, caregiver's belief that full adherence is impossible and caregiver having concerns about loss of privacy had a negative effect on their ability to adhere (Reddington et al. 2000). Similarly, in a study conducted on children with asthma using a previously validated Belief about Medicines Questionnaire, parental concerns about medication were a predictor of poorer adherence (Conn et al. 2005).

3.7.1.3 Social support

Social support has been found to be associated with adherence in HIV disease (Edwards 2006, Gonzalez et al. 2004, Simoni et al. 2002,) and in other health conditions in adult population (Garay-Sevilla et al. 1995). Researchers have reported that this relationship may not be a direct relationship but is mediated through self-efficacy, (Luszczynska, Sarkar & Knoll 2007, Simoni, Frick & Huang 2006, Simoni et al. 2002) Social support, which can be in the form of practical or emotional support, depends on several aspects of an individual's social life including living arrangements, marital status, family cohesiveness and family conflict (DiMatteo 2004). In a study that investigated the relationship between general social support and medication-specific social support with medication adherence in HIV adults, only medication specific social support was found to be correlated with adherence (Warner et al. 2013).

3.7.1.4 Knowledge

Knowledge has been included in the social cognitive theory as a predeterminant of health behaviour (Munro et al. 2007). Nevertheless there has been a lack of conclusive information on the relationship between knowledge and adherence to medication. A study conducted in South Africa on medicines information seeking behaviour among patients with limited literacy showed that such patients had limited medicines-related knowledge (Patel, Dowse 2013). Higher caregiver HIV treatment-related knowledge was found to be significantly associated with undetectable viral load, a proxy for adherence behaviour, and in turn caregiver HIV status was found to be associated with the caregiver's HIV treatment-related knowledge (Nicholson et al. 2006). In another study, HIV treatment knowledge was found to have no relationship with adherence to ARVS (Wolf et al. 2007).

3.7.1.5 Facilitators and barriers to adherence

Munro (Munro et al. 2007) describes other factors that may influence adherence which are presented in the information motivation, behavioural skills model, as factors that relate to

access to medical services, living situation and psychosocial health. He also describes facilitators and barriers to adherence in the social cognitive theory, factors which have a potential to influence adherence. In this study I refer to these factors as ‘external’ factors.

3.8 Summary

Adherence includes taking, as agreed, the correct amount of the medicine each day (‘frequency adherence’) at the prescribed time intervals (‘interval adherence’) and following any dietary recommendations while taking the medication (‘dietary adherence’) (Marhefka et al. 2006b). There has been substantial debate on the use of the three terminologies that refer to the extent to which patients understand and follow the requirements for management of their health conditions, i.e. compliance, concordance and adherence. Globally, sub-optimal adherence levels have been reported for prescribed medication in both the HIC and LMIC (World Health Organisation 2003, Banning 2012, Chacko et al. 2012). Non-adherence to chronic medication does not only result in deterioration of health but has an economic impact on populations and nations as a result of increased hospitalization (McGrady, Hommel 2013) and mortality, and decreased productivity (van Boven et al. 2013).

Interventions to increase adherence to medications have been implemented for many years in the general patient population (Kripalani, Yao & Haynes 2007) and specifically in children (Fielding, Duff 1999, Graves et al. 2010), for both chronic (Kripalani, Yao & Haynes 2007) and short-term conditions (Haynes et al. 2008) but not all adherence interventions result in improved adherence or treatment outcomes (Kripalani, Yao & Haynes 2007).

Adherence to medication can be assessed in multiple ways (Berg, Arnsten 2006, Davies et al. 2008, Hecht 1998, Vreeman et al. 2008b), with some methods being simpler, of lower cost and more clinically applicable, whilst others are more suitable for research purposes (Müller et al. 2011). Methods of assessment may be classified as subjective or objective; the main subjective methods are self-reports that include 24-hour, 2-day, 3-day and 7-day recall of adherence up to 365 days, questionnaires, the VAS, and clinician-reported adherence (Butler et al 2004, Nabukeera-Barungi et al. 2007, Shi et al. 2010a, Simoni et al. 2006). The more objective methods include clinic-based pill counts (Appelgren et al. 2010) or unannounced home-based pill counts (Minzi, Naazneen 2008), pharmacy refill records (Choo et al. 1999), appointment keeping, biological markers such as therapeutic drug monitoring (Mc van

Rossum et al. 2002, Back, Gibbons & Khoo 2006) and electronic drug monitoring of which, in the latter case, the most commonly used is the MEMS[®] (Lyimo et al. 2011, Nabukeera-Barungi et al. 2007, Shi et al. 2010a, Shi et al. 2010b).

Among other criteria, an ideal adherence monitoring tool must be valid and reliable. Evaluation of adherence monitoring tools, however, is complicated by the lack of a gold standard for monitoring patient adherence, since there is no one measure that has been found to be close to perfect and serve as an ideal standard. MEMS[®], despite having some drawbacks as a gold standard, has been widely used as a criterion reference for this type of validation (Müller et al. 2011).

Despite irregularities with all methods of assessing adherence to medication, some methods produce more valid adherence assessment results than others (Müller et al. 2011). Self-reported adherence is the most commonly used of the adherence monitoring methods since it is inexpensive and easy to apply for routine clinical use, especially in resource-constrained settings (Balikuddembe et al. 2012, Berg, Arnsten 2006). Reported adherence provides useful adherence estimates in ART since resulting ART adherence levels have been found to correlate with HIV-1 RNA viral loads and viral rebound (Chesney et al. 2000, Glass et al. 2008, Simoni et al. 2006) and has been found to correlate with other adherence measures (Simoni et al. 2006). However, in some instances, the correlation between reported adherence and viral response has been found to be very weak and this measure has been shown to overestimate adherence levels (Minzi, Naazneen 2008). The low sensitivity of self- and caregiver-reported adherence measures in detecting non-adherence is ascribed to this type of measure as being subject to social desirability and recall biases (Gagné, Godin 2005). Self-report tools that are more accurate can be developed using literature review, input from patients or input from healthcare professionals since techniques for stimulating recall and for reducing social desirability bias in self-reports have been identified (Garfield et al. 2011).

Pill count method is the second most used method of adherence monitoring after self-reports, according to a South African study (Naidoo, Taylor & Jinabhai 2010). The pill count method is considered to be easy to administer and less costly (Martin et al. 2009). However, challenges in using pill counts have been identified, including patients forgetting to bring in remaining pills, keeping pills in another location, and healthcare providers not conducting the pill counts (Appelgren et al. 2010, Martin et al. 2009). Several methods of pill counts have

been described which disclose the ways that were employed to improve the accuracy of pill counts. One of these is to ask patients to bring in all empty, partially full and full medicine containers at the start of the adherence monitoring period and at every visit thereafter (Martin et al. 2009).

Adherence monitoring, counselling and support are critical in any ART programme since non-adherence to treatment has been identified as the main reason for treatment failure (Bangsberg et al. 2001). Viral loads below detectable rates were found to be closely related to adherence levels in children on ART (Elise et al. 2005, Farley et al. 2003a) and in general, lower viral loads and virological response were associated with higher adherence levels (Giordano et al. 2004, Oyugi et al. 2004, Van Dyke et al. 2002,) with adherence being shown to predict long-term virological suppression (Bisson et al. 2008, Ford et al. 2010). In adults, levels of adherence to protease inhibitors of 95% calculated using MEMS[®] and based on the proportion of the prescribed doses that are actually taken, were found to be optimal for virological outcomes (Paterson et al. 2000). Adherence levels below 95% may still be adequate for patients on NNRTI but are not adequate for virological suppression in patients receiving partially suppressive unboosted protease inhibitors (Bangsberg 2006).

Literature shows that adherence levels to ART in children vary widely from 20% - 100% in HIC and from 27% - 100% in LMIC. Adherence varies with the type of adherence tools, age, setting, whether proportions of adherent children or mean adherences are reported and the duration over which adherence is monitored. Studies have identified factors that affect adherence but there is inconclusive evidence on the nature of relationships between these factors and adherence since different studies have shown conflicting findings on which factors positively influence adherence and which ones are associated with poorer adherence.

CHAPTER 4: DESIGNING RANDOMISED CONTROLLED TRIALS

4.1 Randomized controlled trials and adherence tool validation

Randomised controlled trials (RCTs) can be used to compare an experimental product with an existing comparator. When designed in a scientifically sound manner, RCTs are often considered to be the best approach for this purpose. RCTs are frequently used in assessing the effectiveness of adherence interventions (Brian Haynes, Ann McKibbin & Kanani 1996, Kripalani, Yao & Haynes 2007), but have rarely been used in evaluating or comparing adherence monitoring tools. Mannheimer (Mannheimer et al. 2008) used a RCT to compare two pre-existing self-report adherence tools which had different recall periods. In this thesis, due to unaffordability of MEMS[®] and viral load or drug blood level measurements as criterion references, the use of a superiority RCT design in evaluating a new self-report tool using an existing self-report tool as a control, by comparison, is explored. In this methodology I determined whether the new tool would detect a higher number of non-adherent patients than its comparator, based on the findings that self-report tools have low specificity (low capacity to detect all non-adherent patients) and yet have close to perfect sensitivity (classifying all those who are adherent as such) (Müller et al. 2011).

Lack of a gold standard in assessing adherence brings challenges in validating adherence tools (Simoni et al. 2007). Pharmacy refills measure the amount of medication dispensed, MEMS[®] measure the opening of pill containers, pill counts measure the amount of pills removed from the bottle, self-reports are influenced by the informant's recall and willingness to report on the amount of medicines that have been taken, and biological markers measure the amount of drug/metabolite that has reached certain systems/organs in the body. Regardless of these drawbacks, determination of criterion validity of adherence monitoring tools in HIV disease has often been done by using MEMS[®] (Shi et al. 2010a) and virological loads, (Müller et al. 2011) or drug blood levels as criterion reference. The experimental (new) adherence tool, when considered as a diagnostic tool, is compared to MEMS[®] or virological loads and the sensitivity, specificity, positive predictive value and negative predictive value are calculated against these 'not-so-ideal' gold standards (Müller et al. 2011). However MEMS[®], viral loads, or therapeutic drug level measurements often have feasibility or affordability issues due to scarcity of resources and high costs of these measures (Müller et al. 2011). Based on overwhelming evidence pointing to the high sensitivity and low

specificity of the self-reported adherence tools (Müller et al. 2011), differences in adherence levels between two self-report tools can be accredited to improved or decreased specificity as opposed to differences in sensitivity. The improved specificity implies identifying more people who are non-adherent, which is the desired effect of any new self-reported adherence tool, since this method has been critiqued for having lower capacity to detect non-adherence. Based on these characteristics of self-report tools, a superiority randomised control design would be ideal in validating a new self-report tool against current self-report tools, since these are not ideal as gold standards, when the more objective adherence measures are not affordable.

Whilst there are set standards for conducting and reporting RCTs, (Moher et al. 2010) in reviewing clinical standards for trials in HIV treatment, TB treatment and malaria in the sub-Saharan region, it was noted that researchers and ethics committees were taking into consideration the local level of care (Kent et al. 2004). As a result of the concerns raised on the design and reporting of RCTs (Moher et al. 2010), this chapter discusses concepts in the design and reporting of RCTs (Schulz, Altman & Moher 2010) of which relevant ones were used to guide the design of this study. The guidelines in the Consolidated Standards for Reporting Trials (CONSORT) (Schulz, Altman & Moher 2010) statement, and the extension of the previous version of the CONSORT statement to trials that are not of a pharmacological nature (Boutron et al. 2008), were consulted in the reporting of this RTC.

4.2 Conceptual frameworks of randomized controlled trials

The three major conceptual frameworks that guide the design of RCTs (Moher et al. 2010) differ on the aim of the trial regarding the nature of the desired outcome of comparison between the existing comparator and the experimental product. Most commonly, the aim of the trial is to demonstrate that the experimental product is superior to an existing comparator, in which case a ‘superiority’ trial is designed. If the aim is to demonstrate that the experimental product is non-inferior or has an effect that is as good as the comparator, ‘non-inferiority’ and ‘equivalence’ trials are designed, respectively (Christensen 2007).

An understanding of the differences in RCT design is critical to correct interpretation of the findings thereof. The results of a superiority study may be sufficient to demonstrate non-inferiority and the results of a non-inferiority study may be sufficient to demonstrate

superiority. The interpretation of these findings requires knowledge of confidence intervals and how they work to support the conclusions that can be drawn from the results

4.2.1 Superiority trials

A superiority study is conducted when there is a need to demonstrate that the experimental product is superior to the comparator. A superiority statistical test is conducted and if it produces a significant result, it can be concluded that the experimental product is different in effect from the comparator. If the test is in favour of the experimental product, then it can be concluded that the experimental product produces a better effect than the comparator (Lesaffre 2008). Failure to demonstrate a difference in a superiority trial design does not lead to a conclusion of equivalence since there is always some difference in the non-identical products that may, at higher sample size, be adequate to reject the ‘null hypothesis’ of equal effect (Lesaffre 2008).

Steps in designing superiority trials include specifying the ‘null hypothesis’ H_0 , for the statistical test and the corresponding alternative hypothesis H_A , and determining the desired margin by which the experimental product is superior to the existing comparator, which is referred to as the ‘Clinical Significance’ or the ‘Least Relevant Difference’ denoted by the Greek letter Δ . In this case the H_0 specifies that the difference in the effect of the two products Δ , is zero (i.e. $H_0: \Delta = 0$). The corresponding alternative hypothesis is $H_A: \Delta \neq 0$ (Christensen 2007). The ‘null hypothesis’ and the alternative hypothesis are important in interpreting the results of the statistical test whilst the ‘Least Relevant Difference’ has value in calculating the minimum required sample size for superiority trials.

Additional to the ‘Least Relevant Difference’, there are other factors that are considered in sample size calculation of superiority trials (Wittes 2002). The difference in effect between the experimental and control arms is subject to the effect of random factors. The standard deviation denoted in statistical terms by S or the variance S^2 help in describing the magnitude of the variation caused by the random factors.

Even if the ‘null hypothesis’ of no difference in effect between the experimental product and the comparator were not true, a trial may fail to show this difference as a result of random variation. This type of error, that is inherent in trial design, is referred to as a ‘type 1’ error. On the other hand, the trial may show that there is a difference in the effect of the two

products when in actual fact there is none, an error referred to as a ‘type 2’ error. These errors should be minimised when designing RCTs as a ‘type 1’ error can result in failure to introduce a more effective product onto the market when it is available, whereas a ‘type 2’ error can result in introducing an ineffective product onto the market. Whilst in each trial the risk of introducing each of these errors should be assessed to determine the acceptable limits, the generally acceptable limit for the type 1 error, α , is normally set at 0.05 for a two tailed test and the ‘type 2’ error, β , is normally set at 0.1 to 0.2. It is desirable to set the limits for these errors as close to zero as possible, but this does demand large sample sizes. The above-mentioned limits have been necessitated by limitations in resources when conducting clinical trials (Christensen 2007, Lesaffre 2008).

The test statistics that are commonly used in superiority trials include the chi-square test and corresponding p-values and two sided 95% CI, or the unpaired t test for comparing means (Lesaffre 2008). When the 95% CI of the difference Δ does not include zero or when the p-value is less than that of the set limit (e.g. 0.05 for the two tailed test) then the ‘null hypothesis’ of no difference can be rejected and it can be concluded that the experimental product and the comparator are statistically significantly different in their effect. Otherwise, we can conclude that the trial did not show any evidence for a difference in effect between the experimental and the comparator.

4.2.2 Non-inferiority trials

The purpose of non-inferiority trials is to demonstrate that the experimental product is at least as effective as the comparator. This is often useful when the experimental product has other advantages over the existing comparator such as safety, cost or dosing intervals that promote adherence to the treatment regimen (D'Agostino, Massaro & Sullivan 2003).

The important parameter in the design of non-inferiority trials is the non-inferiority margin, M , a measure of how much the effect of the comparator can exceed the effect of the experimental product without the experimental product being considered inferior (D'Agostino, Massaro & Sullivan 2003, Lennox et al. 2009). Considering a comparator with an effect C and an experimental product with an effect E , the ‘null’ and the alternative hypotheses in a non-inferiority study are as follows:

$H_0: C-E \geq M$ (implying C is superior to E)

$H_A: C-E < M$ (implying E is not inferior to C)

When the ‘null hypothesis’ is rejected through a statistical test, then the experimental product is considered to be non-inferior to the comparator. Means or proportions can be used for the statistical test by conducting a one-sided hypothesis test at α level of significance or computing a two-sided CI for the difference, C-E at 100 (1-2 α) percent confidence level. In the former the ‘null hypothesis’ is rejected when the calculated p-value $< \alpha$ and in the latter the ‘null hypothesis’ is rejected when the upper limit of the CI $< M$, at an α level of significance (Chan 2003, D'Agostino, Massaro & Sullivan 2003, Lennox et al. 2009).

4.2.3 Equivalence trials

A value of the difference in the effect between the comparator, C and the experimental product E, Δ_E , can be established for which in practice it would be considered that the two products are still equivalent with regard to the desired effect. In this case the two products are considered equivalent if the point estimate of the observed difference, Δ , and its two-sided 100(1-2 α) CI lies between $-\Delta_E$ and $+\Delta_E$, thus rejecting the ‘null hypothesis’, $H_0: \Delta < -\Delta_E$ or $\Delta > \Delta_E$ (Lesaffre 2008, Chan 2003). The alternative hypothesis, $H_A: -\Delta_E \leq \Delta \leq \Delta_E$ thus stands true.

4.3 Single or multiple centre trials

RCTs can be conducted in a single centre (Nachega et al. 2010) or in multiple centres (Lennox et al. 2009, le Roux et al. 2009, Moodley et al. 2003). Multiple centres are often an option when there is a need to increase enrolment or to improve generalizability of the results to the population. A single centre may be necessary to reduce cost and to minimize requirements of logistical arrangements.

4.4 Primary and secondary endpoints

The outcome that most accurately reflects the benefit of the experimental product is referred to as the primary endpoint and is usually linked to the main objective of the RCT (Moodley et al. 2003). Other outcomes of interest relating to the experimental product and often reflecting its success or failure, such as side effects or timing of the onset of the effect of the experimental product, are categorized as secondary endpoints (Moodley et al. 2003, Petrie

2009). The primary endpoint is often the most important factor to be considered in determining the 'clinical significance' that is used in calculating the sample size. However, there might be a need to determine the optimum sample size by considering other important secondary endpoints.

4.5 Subgroups

If an analysis of the results of a RCT is to be stratified by some patient characteristics, these have to be considered in calculating the sample size when the power of a trial to detect a difference between the experimental product and the existing comparator is to be maintained at a predetermined level. Stratifying analysis of results by patient characteristic has an effect of reducing the sample size hence reducing the power of the study. If the minimum sample size was not calculated considering these different subgroups, then the sample size of each group falls below the minimum sample size required to detect the differences in desired effect between the two arms of the trial at a given confidence level (often set at 95%) (Christensen 2007, Petrie 2009).

4.6 Parallel, cross-over and factorial designs

A parallel design in a RCT is one whereby study participants are randomized into two or more arms in which the experimental product and the comparator are used and the effect measured concurrently (Chan 2003). In some clinical trials, study participants act as their own control by introducing a washout period in between. This approach, called a cross-over design, is appropriate in interventions that involve products whose effect can be reduced to nil during the washout period (Chan 2003).

A factorial design involves randomization of study participants in such a way that they receive two or more products separately, in combination and against a control (le Roux et al. 2009). An example is a 2 x 2 factorial design in which four sets of data are generated for analysis (Teri et al. 2011, Thior et al. 2006). The data is for participants who received product A, those who received product B, a third group who received product A and B and those who received neither A nor B (Stolberg, Norman & Trop 2004).

4.7 Randomisation

Randomisation in clinical trials is a process of randomly allocating patients into treatment arms (or comparison arms) such that each patient has the same probability of being allocated to each arm. When adequately randomized, patient characteristics should be comparable and any differences should be due to chance only. For this reason, Petrie and Sabin (2009), in their book, *Medical Statistics at a Glance*, discourage the use of a formal statistical hypothesis test to compare the parameters of baseline characteristics in a trial, arguing that this hypothesis test would be assessing whether the observed difference between the groups is due to chance.

Stratified randomization helps to control for potentially confounding factors such as age by ensuring that these factors are equally distributed between the trial arms. Block or restricted randomization is performed by using a modified form of randomization that creates small blocks of numbers in multiples of the number of trial arms. Equal numbers of patients are then allocated to each arm within each block. Cluster randomization (Majoko et al. 2007) involves allocation of a group (or cluster) of individuals to a treatment arm where splitting individuals within a group is not possible or impractical, or when there is a possibility of cross contamination on the outcomes between individuals in the trial arms.

4.8 Blinding

Blinding (or masking) is a way of minimizing assessment bias arising from either patient or clinician/assessor awareness of the trial arm allocation. When all the above categories are masked, this is referred to as double blinding (Lennox et al. 2009) whereas when the three groups are not masked, the trial is referred to as an open label trial (Collier et al. 2005, Gross et al. 2009, Nachega et al. 2010). If it is possible to mask one of these groups but not the other, the type of blinding is referred to as single-blinding (Teri et al. 2011).

4.9 Protocol deviations

A patient may enter a trial, be randomized to a trial arm but may ultimately fail to fulfil the criteria set out in the trial protocol, for example switching treatment or failing to complete the study. One way is to analyse data on all patients who have information within the groups to

which they were initially allocated, regardless of whether they followed the protocols within this group or not i.e all randomized patients. This approach to the analysis of RCT data is known as analysis by intention-to-treat (Heritier, Gebski & Keech 2003, Kruse et al. 2002, Nachega et al. 2010). On treatment or per-protocol analysis includes only those patients who complete treatment, complying with the protocols as closely as possible without major deviations (Lennox et al. 2009). The drawback of this type of analysis is that it can introduce bias through those who are excluded (Heritier, Gebski & Keech 2003). A third approach in analysing RCT data is treatment received in which all patients are analysed based on the type of treatment they received. Even with this approach the effect of random allocation is compromised (Heritier, Gebski & Keech 2003).

4.10 Summary

Randomised controlled trials (RCTs) can be used to compare an experimental product with an existing comparator. When designed in a scientifically sound manner, RCTs are often considered to be the best approach for this purpose. RCTs have rarely been used in evaluating or comparing adherence monitoring tools. In this thesis, due to unaffordability of MEMS® and viral load or drug blood level measurements as criterion references, the use of a superiority RCT design in evaluating a new self-report tool using an existing self-report tool as a control, by comparison, is explored. In this methodology I determined whether the new tool would detect a higher number of non-adherent patients than its comparator, based on the findings that self-report tools have low specificity (low capacity to detect all non-adherent patients) and yet have close to perfect sensitivity (classifying all those who are adherent as such) (Müller et al. 2011).

As a result of the concerns raised on the design and reporting of RCTs (Moher et al. 2010), this chapter discusses concepts in the design and reporting of RCTs (Schulz, Altman & Moher 2010) of which relevant ones were used to guide the design of this study. The guidelines in the Consolidated Standards for Reporting Trials (CONSORT) (Schulz, Altman & Moher 2010) statement, and the extension of the previous version of the CONSORT statement to trials that are not of a pharmacological nature (Boutron et al. 2008), were consulted in the reporting of this RTC.

The three major conceptual frameworks that guide the design of RCTs (Moher et al. 2010) differ on the aim of the trial regarding the nature of the desired outcome of comparison between the existing comparator and the experimental product. Most commonly, the aim of the trial is to demonstrate that the experimental product is superior to an existing comparator, in which case a ‘superiority’ trial is designed. If the aim is to demonstrate that the experimental product is non-inferior or has an effect that is as good as the comparator, ‘non-inferiority’ and ‘equivalence’ trials are designed, respectively (Christensen 2007).

A superiority study is conducted when there is a need to demonstrate that the experimental product is superior to the comparator. A superiority statistical test is conducted and if it produces a significant result, it can be concluded that the experimental product is different in effect from the comparator. The test statistics that are commonly used in superiority trials include the chi-square test and corresponding p-values and two sided 95% CI, or the unpaired t test for comparing means (Lesaffre 2008). If the test is in favour of the experimental product, then it can be concluded that the experimental product produces a better effect than the comparator (Lesaffre 2008). Failure to demonstrate a difference in a superiority trial design does not lead to a conclusion of equivalence since there is always some difference in the non-identical products that may, at higher sample size, be adequate to reject the ‘null hypothesis’ of equal effect (Lesaffre 2008).

RCTs can be conducted in a single centre (Nachega et al. 2010) or in multiple centres (Lennox et al. 2009, le Roux et al. 2009, Moodley et al. 2003). Multiple centres are often an option when there is a need to increase enrolment or to improve generalizability of the results to the population. A single centre may be necessary to reduce cost and to minimize requirements of logistical arrangements.

The outcome that most accurately reflects the benefit of the experimental product is referred to as the primary endpoint and is usually linked to the main objective of the RCT (Moodley et al. 2003). The primary endpoint is often the most important factor to be considered in determining the ‘clinical significance’ that is used in calculating the sample size. However, there might be a need to determine the optimum sample size by considering other important secondary endpoints. If an analysis of the results of a RCT is to be stratified by some patient characteristics, these have to be considered in randomisation and in calculating the sample size when the power of a trial to detect a difference between the experimental product and the

existing comparator is to be maintained at a predetermined level. When adequately randomized, patient characteristics should be comparable and any differences should be due to chance only. Stratified randomization helps to control for potentially confounding factors such as age by ensuring that these factors are equally distributed between the trial arms. A parallel design in a RCT is one whereby study participants are randomized into two or more arms in which the experimental product and the comparator are used and the effect measured concurrently (Chan 2003). Blinding (or masking) is a way of minimizing assessment bias arising from either patient or clinician/assessor awareness of the trial arm allocation.

CHAPTER 5: METHODOLOGY

5.1 Introduction

This chapter describes the design of an single blinded, two arm, dual centre, parallel superiority design RCT which was conducted for the evaluation of a newly-developed visually- and verbally-cued self-reported adherence monitoring tool for assessment of adherence in children who were receiving ART at two sites in Zimbabwe.

Two pill count methods were compared and assessed for their feasibility and accuracy in routine monitoring of adherence to ARV treatment in children in my study settings. Based on previous studies highlighting challenges with the quality of pill count data (Appelgren et al. 2010, Martin et al. 2009), the percent discrepancy in pill counts, a measure assessing both medication-taking and medication-handling behaviour, was formulated and used to assess feasibility and accuracy of this method. Factors associated with non-adherence in children were identified using reported adherence and challenges and barriers to adherence and reporting non-adherence were identified using the qualitative focus group approach. Table 5.1 below summarises the objectives and methods that were used to meet these objectives.

Table 5.1: Summary of methods used to address specific objectives in this study

Objective	Summary methods	Main outcome measures
Establish levels of adherence to ART in children and identify factors associated with adherence and challenges to adherence.	Cross-sectional study with calculated minimum sample size of 55 children ≥ 10 years of age and 110 children less < 16 years of age for each self report-tool was used to determine factors associated with adherence. This quantitative information was complemented with qualitative data from focus group discussions that were used to identify challenges to adherence. A calculated sample size of 126 child-caregiver diads was the minimum required sample size for prevalence study to establish adherence levels in children using reported adherence at 95% confidence level and 5% confidence limit.	Adherence levels assessed by both child and caregiver reports using past 7 days child and caregiver reports and the MMAS-8.
Design and conduct an initial evaluation of a 'past 10 days' visually- and verbally-cued self-reported adherence monitoring tool.	Single blinded, dual centre parallel superiority design randomized controlled trial with calculated minimum sample size of 60 children ≥ 10 years of age in each arm for purposes of adherence monitoring using the child reports in this age group and hence 120 child-caregiver pairs in each randomised arm including 60 for those children below 10 years age. The minimum sample size for the combined groups was 240.	Adherence levels by the new 10-Day tool and PACTG-style tool. Concurrent validity with MMAS-8 and inter-rater reliability within child-caregiver diads.
Assess the feasibility of using pill count methods in the study settings.	The feasibility of using the pill count method of adherence monitoring was assessed in all the 246 children who were recruited in a study to evaluate a new self-report tool. This number was adequate to cover the minimum sample size of 87 children for the determination of proportion of children who return medication to the health facility at 95% confidence level and 5% confidence limit. This calculation was based on an SA study that showed that 94% of children would return their medication to the clinic (Davies, 2008).	Proportion of children with information for computing pill count adherence and discrepancy between the expected and actual quantity of medication returned to the clinic. Concurrent validity with reported adherence.
Identify barriers to reporting adherence accurately.	Qualitative study using the focus group approach with two child groups and three caregiver groups.	Challenges in accurate reporting of adherence and barriers to accurate disclosure of non-adherence.

5.2 Study setting

The study was conducted at two sites. The first site, Harare Children's Hospital, is part of Harare Central Hospital, an urban tertiary health institution that is wholly owned and operated by the Government of Zimbabwe. The hospital is linked to the University of Zimbabwe and serves as a university teaching hospital, offering specialist services. Harare Children's Hospital was one of the first few sites to offer paediatric ART in the country. ART services for children were at roll-out stage at the time when the study was conducted.

The second site, Murambinda Mission Hospital, is a rural, faith-based secondary health facility that is situated approximately 250 kilometres to the south-east of Harare. The hospital is managed by the Catholic Church in conjunction with the MoHCW. HIV and AIDS services at the hospital are supported by multiple donor and supporting organisations. Médecins Sans Frontières is the major supporting organisation in the provision of ART services. The hospital was rolling-out and decentralising its ART services to the surrounding primary health facilities at the time of the study.

At both sites HIV positive children referred from the lower level health facilities and those within the catchment area of the health facilities visit the OI/ART clinics for treatment of opportunistic infections and initiation of ART as appropriate. Those who are eligible for ART according to the current Zimbabwe national ART guidelines are initiated on treatment and provided with appropriate follow-up services. Ideally, children visit the OI/ART clinics accompanied by their caregivers.

5.3 Study hypothesis

The research hypothesis was that the newly-designed adherence monitoring tool, which measures adherence in the 'past 10 days' and has visual and verbal cues to help the reporter to recall adherence behaviour, should allow children or caregivers to report adherence more accurately by providing better estimates of adherence levels using reported adherence (i.e. have higher specificity in measuring adherence) than current self-report tools that are based on the AIDS Clinical Trials Group (ACTG) adherence tools (Chesney et al. 2000, Van Dyke et al. 2002). The ACTG adherence tools were developed by the Outcomes Committee of the AIDS Clinical Trials Group, sponsored by the NIH/NIAID and the PACTG sponsored by

NIH/NIAID/NICHD. The Outcomes Committee promotes the use of these tools in other projects. Currently used ACTG adherence behaviour tools consist of questions asking about the number of doses missed in a specified period of time prior to adherence assessment e.g. Day 1, Day 2 and Day 3, Day 4, ‘past 7 days’, 14 days or 30 days for each ARV.

5.4 Adherence monitoring methods and tools

Two methods of assessing adherence were used: reported adherence by child and caregiver, which are subjective measures and return pill count, which is an objective measure.

5.4.1 Existing self-reported adherence monitoring tools

Reported adherence was assessed using a slightly modified version of the PACTG Adherence Questionnaire Module 1-III (the modified tool is hereafter referred to as the ‘PACTG-style tool’) (Appendix 1) in the control group. The modification on the original tool was that the researcher introduced the medicines being taken through samples of tablets, and confirmed the identification of the medicines with the respondent. In the original tool the respondent is given an opportunity to volunteer the names of the medicines or is prompted to give the names of the medicines after which the interviewer provides information on any un-identified medicines. The modification was done to reduce interview time. Additional to the ‘past 3 days’, adherence was assessed for the ‘past 7 days’, 14 days and 30 days. Data collectors were instructed to replace the words HIV with the words “health condition” when assessing adherence in children ≥ 10 years of age in cases where HIV status was not disclosed to the child.

The MMAS-8 (Morisky et al. 2008) (Appendix 2) and the VAS (Amico et al. 2006), both validated adherence monitoring tools, were used in all participants for purposes of validating the experimental tool.

5.4.2 Development of the new 10-day self-reported adherence monitoring tool

Using several techniques for improving self-report measures of non-adherence suggested by Gagné, Godin (2005), a new visually- and verbally-cued, clinically-applicable self-reported adherence monitoring tool (hereafter referred to as the ‘new 10-day tool’) was developed (Appendix 3). The ‘new 10-day tool’ assesses self-reported adherence for each day in the ‘past 10 days’. In the study population that was taking ARV medication on a twice daily

basis, 10 days is the minimum period that is required to measure non-adherence using the adherence threshold of having taken at least 95% of all prescribed doses, implying 20 doses in 10 days. With a period of less than 10 days of adherence assessment on a twice daily dosage interval and an adherence threshold of having taken at least 95% of the prescribed doses, only those people who are 100% adherent would be classified as adherent. On a twice daily ARV regimen, if a patient misses one dose in the 10 days then s/he is still adherent even though not 100% adherent, but missing more than one dose in the 10 days can be classified as non-adherence. Assessing adherence for fewer doses than 20 presents challenges in using the 95% adherence threshold since missing one dose automatically implies adherence levels below 95%. This implies that all those who are <100% adherent will also be classified as less than 95% adherent.

5.4.2.1 Verbal cues in the ‘new 10-day tool’

Whilst recall of adherence has been found to be better with shorter periods such as four days (Levine et al. 2006), a moderately longer period of 10 days with specific reference time periods of recall (such as “this week” and “last week”) and reminder events or activities to aid recall were used. Techniques for reducing social desirability bias were employed in the tool and these included; making the respondent feel that non-adherence is normal (although not desirable), assuring confidentiality and assuring unbiased subsequent services when non-adherence is reported.

5.4.2.2 Visual cues in the ‘new 10-day tool’

Pictures of scored pills were included in the tool with morning and evening doses placed below pictures of the rising sun and a moon in a darkened environment to denote morning and evening times, respectively, as illustrated on some plastic bags into which tablets are dispensed (Figure 5.1). This aimed to help the respondent identify and record how much of the medication was not taken as the respondent was required to shade in the missed pills which the healthcare worker would translate into proportion of doses missed. In this way the tool captures information on non-adherence resulting from taking partial doses, without the need for the patient to mention specific ARVs and the patient takes part in the recording of non-adherence behaviour. It was anticipated that this would help minimize the effects of recall bias and the effects of low literacy in reporting past adherence behaviour, since specifically identifying individual ARVs was found to be problematic in some populations (Gagné, Godin 2005).

Day (Zuva revhiki)	Morning dose (Mapiriti anomwiva mangwanani) 	Evening dose (Mapiriti anomwiwa manheru) 	Interviewer comment
Saturday Mugovera			
Sunday (this week) Svondo			
Monday Muvhuro			
Tuesday Chipiri			
Wednesday Chitatu			
Thursday China			
Friday Chishanu			

Figure 5 2: Visual cues in the ‘new 10-day tool’

This single tool captured most of the information that different previously designed adherence questionnaires have attempted to capture through several items (Byerly, Nakonezny & Rush 2008, Deschamps et al. 2008). In addition it assessed medication non-adherence for each individual day in the ‘past 10 days’ using a week and weekend days as time markers and reminders. A weekend event is used as a time marker and reminder to aid recall of the activities and related adherence behaviour during that week. Through the shading of missed doses on each day of the week, one is to identify specific days that present the most adherence challenges and relate them to the child/caregiver’s activities. In addition to the

verbal cues, the tool allows the person reporting non-adherence to put more thought into the report as s/he participates in shading the number of doses not taken.

5.4.3 Pill counts

In my study sites, ‘routine pill counts’ were done by considering only the quantity of medication that were brought to the clinic and the quantity that was dispensed at the previous visit, assuming that there was no medication that remained at home at the previous dispensing (i.e. residual quantity at last refill). Under this assumption of no ‘residual quantity’ (RQ) of medication at last refill, the routine formula for pill count method (Appelgren et al. 2010, Martin et al. 2009) which in this thesis will be referred to as ‘routine pill count’, is:

$$\text{'Routine Pill count'} = \frac{\text{\# of pills dispensed} - \text{\# number of pills returned}}{\text{\# of elapsed days between dispensing and returning date} \times \text{\# of pills prescribed per day}} \times 100$$

A second pill count method was designed to capture any amount of medication that was not brought to the health facility at the last refill, hereafter referred to as the ‘Residual Quantity’ at last refill. This method relied on caregiver-‘reported residual quantity’ (RRQ) of pills at the last refill (referred to as ‘Pill count RRQ’ in this study) since there was no available record for this information. In this study the formula that was used for pill count adherence levels using this second method is:

$$\text{'Pill count RRQ'} = \frac{(\text{\# of pills dispensed} - \text{\# number of pills returned}) + \text{residual quantity at last refill}}{\text{\# of elapsed days between dispensing and returning date} \times \text{\# of pills prescribed per day}} \times 100$$

A measure of assessing patient behaviour that combines both adherence and medication-handling behaviour was formulated for this study. The measure is the percent discrepancy in the quantity of returned medication, which is a measure of the extent to which the medication returned to the clinic deviate from that expected at that visit, taking into account the period that has lapsed between dispensing and returning to clinic and ignoring whether the discrepancy is positive (more medication is returned) or negative (less medication is returned) a concept similar to that used in the calculation of percentage error. This measure can be taken to reflect the non-adherence rate regardless of the direction of the non-adherence behaviour (whether it reflects taking either more or less pills) or any pill handling behaviours that convey a false impression of these adherence behaviours.

The percent discrepancy in ‘Pill count RRQ’ was formulated as follows:

$$\begin{aligned} &\text{Percent discrepancy in 'Pill count RRQ'} \\ &= 1 - \frac{|(\# \text{ of pills dispensed} - \# \text{ number of pills returned})| + \text{residual quantity at last refill}}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100 \end{aligned}$$

The corresponding percent discrepancy in ‘routine pill count’ method is given by the formula:

$$\begin{aligned} &\text{Percent discrepancy in 'routine pill count'} \\ &= 1 - \frac{|(\# \text{ of pills dispensed} - \# \text{ number of pills returned})|}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100 \end{aligned}$$

Pill count data was collected using a form that was designed for this study (Appendix 4).

5.5 Questionnaire development

The questionnaire (Appendix 5) included socio-demographic information of the child and that of the primary caregiver, information on the child’s socio-economic circumstances, ART-related care information and elements of theoretical models that influence behaviour such as caregivers’ medication adherence self-efficacy, beliefs about medicines, social support, respondent caregivers’ knowledge of ART and ‘external factors’. These previously validated constructs (Gatti et al. 2009, Costa et al. 2008) of theoretical models of behaviour change were used in this study both to assess their relationship with adherence measured by currently used methods of adherence monitoring and with the ‘new 10-day’.

The child’s medical history, treatment and any other concurrent medications being taken were recorded on the questionnaire using information from both the medical records and caregiver reports (Appendix 5). The child’s medical history included period since first HIV diagnosis, past ARV regimens, period on ARV, admission history, and any other ART-related information.

5.5.1 Self-efficacy

The self-efficacy questionnaire consisting of 30 items was pre-tested prior to its inclusion in the main questionnaire including valid items from the self-efficacy expectancy scale that was validated by Costa et al (2008) in parents and carers of adolescents and children with

HIV/AIDS in Brazil. The remaining items were developed for use in this study with the guidance of HIV-medication adherence self-efficacy scales that had been used in other studies (Gozum, Hacıhasanoglu 2009, Johnson et al. 2007, Nicholson et al. 2006, Ogedegbe et al. 2003).

Responses to the self-efficacy items were on a five-point scale from 0 to 4: 0 - I definitely will not be able to, 1 - I do not think I will be able to, 2 - do not know, 3 - I think I will be able to and 4 - I definitely will be able to.

5.5.2 Knowledge

Caregiver ART-related knowledge was assessed including names of medicines the child was taking (proprietary or non-proprietary), dose and dose interval, and knowledge of treatment-related aspects such as the meaning of the CD4 count, viral load and resistance (Wolf et al. 2007).

5.5.3 Beliefs about medications

The beliefs about medicines assessed in this study were largely informed by the Beliefs about Medicines Questionnaire originally presented by Horne and Weinman (1999) and also used by Gatti et al (2009) in their study on relationships between beliefs about medicines and adherence.

5.5.4 Social support

Social support was evaluated using seven items designed for this study by the principal researcher, which were regarded as necessary and unique to a caregiver of a child on ART.

5.5.5 ‘External’ factors influencing adherence

Perception of the caregiver on ‘external’ factors that could affect adherence was assessed using nine items designed for this study by the principal researcher. These included accessibility and affordability of ART services and perceptions on the quality of care provided to the child including caregiver-healthcare-provider interactions and child-caregiver relationships.

5.6 Study population

The study was conducted among children below the age of 16 years who were visiting Harare Children's Hospital and Murambinda Mission Hospital for review and refill of ART medication, and their caregivers.

5.6.1 Inclusion and exclusion criteria

5.6.1.1 Inclusion criteria

All children below 16 years of age visiting the two study sites during the one month of data collection for either review or refill of their ART medication. Only the first child of any caregiver to present at any one clinic was included.

5.6.1.2 Exclusion criteria

The following criteria were used to exclude children from the study:

- Children who were not accompanied by either a primary or a secondary caregiver since only these two could be respondents to the interviews.
- Children who were visiting the health facility for the first time during the recruitment period without a caregiver or with a caregiver other than their guardian since only a guardian of the child was expected to give written consent to participate in the study.
- Children who were initiating ART on the day of recruitment.
- Children brought by a caregiver who had not been staying in the same household as the child for at least 30 days. The caregiver in this case would not have accurate adherence history.
- Children whose caregiver came to collect medication without the child.
- Children who had participated in the pre-testing of the questionnaire for this study.
- Children visiting the hospital only for CD4 enumeration since they would not bring their return pills along with them for such a visit.
- Children who were critically ill and or needed hospitalisation on the day of recruitment.

5.6.2 Definition of primary and secondary caregiver

In a study conducted in South Africa, a primary caregiver was defined as a person who has consistently assumed responsibility for the housing, health or safety of the child (Reddi et al.

2007). In my study setting, an individual may be responsible for the housing but may not have much to do with the child's medication-taking. For the purposes of recruiting caregiver interviewees into this study and obtaining consent for the child to participate in the study, we defined a primary caregiver as a person above the age of 18 years who was most (or primarily) responsible for the child's daily welfare and medication-taking and ensures that the child keeps all clinic appointments. Correspondingly, a secondary caregiver in this context was any other person in the household who was above the age of 18 years who assisted the primary caregiver in caring for the child and had a role in the child's medication-taking but is less responsible for the child's medication-taking than the primary caregiver. However, considering that there are child headed households, the age limit would not apply to questionnaire items regarding non-interviewee primary and secondary caregivers.

5.7 Main outcome measures

The main outcome measures for the study were adherence levels assessed by both child and caregiver reports using a 'new 10-day tool' in the experimental group and the 'PACTG-style tool' in the control group. Adherence in all study participants was also assessed by two pill count methods and the MMAS-8. Secondary outcome measures used as proxy for adherence levels included total scores on constructs of theoretical models such as beliefs about medicines, self-efficacy and social support.

5.8 Ethical considerations

Approval to proceed with the study was sought from the study institutional health authorities and from the MoHCW (Appendices 6 and 7) and ethical clearance was obtained from the Medical Research Council of Zimbabwe (Appendix 8) and from Rhodes University's Ethical Standards Committee (Appendix 9). A letter of support was obtained from the Zimbabwe Ministry of Health and Child Welfare (Appendix 10). Written consent was sought from caregivers of all children and assent from children aged 7 years and above (Appendix 11).

The same codes that were used to identify patients in the paediatric ART clinic were linked to a different set of IDs that were used in the study. The list linking these two sets of IDs was kept confidentially by the research team and was used solely for the purposes of the study. Completed questionnaires were stored by the data collectors in a secure, confidential place

during the period of data collection and were eventually all handed over to the custodianship of the principal researcher. Only the data collectors, data capture personnel, the statisticians who assisted with data analysis and the researchers had access to data that was kept by the researcher for specific research-related purposes.

All interviews and FGDs were conducted in a private room or a secluded place where no other individuals that were not involved in the particular discussion group or interview would hear the content of the conversations.

All participants that were found to be non-adherent were informed about the importance of adherence and the risk of non-adherence after the interviews. Each study participant pair (caregiver and child) received R20 (~ US\$2), currencies that were at the time currently acceptable for trade in Zimbabwe, which was equivalent to a return fare for a single local trip for two people. This partly compensated for the time they gave to this study. For those who participated in the FGDs, this amount was doubled in accordance with an increased time commitment to the study.

5.9 Training of data collectors

Two groups of data collectors were trained by the principal researcher. The first group included two doctors who were trained in August 2009 and who conducted pre-testing of questionnaires with the principal researcher, following training. The second group was trained in November 2009 and included one hospital dietician and two medical students who had completed three years of clinical studies at the University of Zimbabwe.

The training of data collectors comprised a two-day training session that was conducted by the principal researcher. During the training, the trainees and the trainer reviewed all data collection tools as a team. At the end of the training session, each data collector was issued with detailed notes and instructions on the data collection process including:

- Background notes
- Inclusion and exclusion criteria
- Flow chart on the data collection process
- List of key points on obtaining consent
- Eligibility checklist

- A short form that included information to be collected on those who decline to participate in the interviews (this was to be used to check if there was non-response bias introduced in the event that there would be a large non-response rate)
- Samples of the data collection tools.

5.10 Pre-testing of data collection tools

In August 2009, the principal researcher and two trained data collectors who were both medical doctors, conducted the pre-testing of all data collection tools in 10 child-caregiver dyads at Harare Children's Hospital, since permission to pre-test the questionnaire at a neighbouring hospital with similar settings was not granted. The protocol established for this study was followed during pre-testing of data collection tools and this included screening of clients, consent seeking, interviewing and administering of the adherence tools.

The following aspects were considered for each question during the pre-testing:

- understanding of questions including scrutinising item wording and identifying possible multiple meanings
- questions that had multiple ideas
- words that were not familiar to the population under study
- responses to ensure that they were mutually exclusive and exhaustive

For items from constructs of theoretical models that influence behaviour the following was noted:

- items that had a high non-response rate (respondent can keep quiet or expresses uncertainty)
- items to which respondents gave the same response

We also measured average time to complete the questionnaire and adherence tools and assessed respondent's satisfaction with the time taken to complete the interview. The average time taken for the interviews was 52 minutes with a maximum of 1 hour 20 minutes and a minimum of 30 minutes. Three of the ten respondents felt that the time taken for the interviews was too long whilst the remainder indicated that the time was satisfactory.

Following pre-testing of the data collection tools, the team that pre-tested the tools held a meeting to discuss findings and give recommendations to the principal researcher on the aspects in the tools that needed revision.

5.10.1 Questionnaire

The following changes were made to the questionnaire:

- Space recording starting and finishing times for the interviews was inserted at the beginning of the questionnaire.
- The randomization groups were described as Group 1 and Group 2 as opposed to just 1 and 2.
- There was no provision for collecting socio-demographic characteristics of secondary caregiver. Since some of these were respondents in this study, this was included in the revised questionnaire.
- It was noted during pre-testing that there was no question on disclosure of HIV-status to the child. This was included in the revised questionnaire.

5.10.1.1 Beliefs about medicines

Initially the 11 items on the Beliefs about Medicines Questionnaire were adapted for use in caregivers of children on ART and the seven specific items from this questionnaire were used in the original form (Horne 2006, Gatti et al. 2009). An additional six items on beliefs about ART were designed in this study specifically for use in my study context (Appendix 5). After pre-testing of the questionnaire, five of the adapted specific items, four of the general items of the Beliefs about Medicines Questionnaire (Horne 2006, Gatti et al. 2009) and three of those formulated for the first use in this study were retained in our questionnaire to assess beliefs about medicines in general and those specifically relating to ARV medication. The remainder of the items on the Beliefs about Medicines Questionnaire were eliminated following pre-testing of the questionnaire if they were poorly understood, sounded to be a repetition of other items in their meanings in the local context, had a double meaning in the local context and had the same rating from all respondents.

5.10.1.2 Perceived social support

All the seven perceived social support items developed for first time use in this study were retained following the pre-testing of the questionnaire.

5.10.1.3 External factors influencing adherence

All initial nine items were retained following pre-testing of the questionnaire.

5.10.1.4 Self-Efficacy

Following the pre-testing of the questionnaire only 18 of the original 30 items were retained, including 11 items from the list of items that had been validated by Costa et al (2008). The remainder were either poorly understood, sounded to be a repetition of other items in their meanings in the local context, had a double meaning in the local context or had the same rating from all respondents.

5.10.2 Adherence monitoring tools

Initially the VAS was included for measuring adherence but was later excluded after the pilot study. It was noted during the pilot study that administering too many tools and asking about adherence using several tools to the same individuals was monotonous and caused exhaustion of the interviewees.

The pill count tool as well as the three self-reported adherence monitoring tools, the ‘PACTG-style tool’ and the ‘new 10-day tool’, and the MMAS-8 were found to work well.

5.11 Introduction of the project to the hospital and clinic teams

The head of the Paediatrics Department at the University of Zimbabwe, who is also a clinician working at the Harare Children’s Hospital, assisted the principal researcher in introducing the research project to the Harare Children’s Hospital senior staff. This was followed by an official meeting with staff at the paediatric OI/ART clinic to mark the beginning of data collection and further introductions of the research project to the rest of the staff members. At the rural site, the district medical officer introduced the team to the staff working at the OI/ART clinic and to the staff at organizations that are supporting OI/ART services.

5.12 Data collection

The principal researcher supervised the data collection activities whilst two of the data collectors assisted in the coordination of data collection activities at each of the two sites.

5.12.1 Dates for data collection

Data collection commenced at Harare Children's Hospital on 9 November 2009 and continued for two weeks before data collection was initiated at the second site, Murambinda Mission Hospital, on 25 November 2009. This was done so that the process could run smoothly and to ensure that quality data were being collected at the first site before expansion to the second site. The first week of data collection was characterized by intensive monitoring, support and supervision on how the data collection tools were administered. Data collection at each site continued for four weeks.

5.12.2 Screening of participants

Screening was applied at the first universal entry point, as illustrated in Figure 5.2 below, for each hospital using an eligibility checklist. Screening was conducted by one of the data collectors. During screening, eligible children and their caregivers were invited to see one of the data collectors as soon as they had finished receiving their medical services for the day and before going to pharmacy to collect their medication. A code known by research staff and pharmacy staff only was inserted on the child's records to enable the pharmacy staff to refer all eligible child-caregiver dyads to the data collection office if they had missed the interviewing processes.

5.12.3 Sampling procedures

Information collected from the two study sites for the preceding three months prior to data collection showed that on average 59 children on ART under the age of 16 years were seen at Murambinda hospital and three of its satellite clinics that were conveniently sampled for data collection every week, giving a monthly average of 236 children. At Harare Children's Hospital, an average of 640 children on ART was seen per month for the three months prior to the implementation of the study. It was also noted that some of the visits by these children were for CD4 measurement, some children would come to the facility twice a month if they had just initiated ART, and other children would come without their caregivers, whilst other caregivers came to collect medication without the children. In order to meet the target for the sample size in the two institutions, which was approximated to take just below a month, there was a need to employ consecutive sampling on all eligible children until our minimum sample size was reached. We also needed to avoid a data collection period exceeding one month since a large proportion of clients visit the health facilities once every month. Entering

into a second month of data collection would result in data collectors encountering a large proportion of those already interviewed in the previous month.

5.12.4 Consent seeking and recruitment

Following screening for eligibility, data collectors recruited patients from the waiting benches outside the data collection rooms within the OI/ART clinic for consent seeking. Signed consent for the child to participate in the study was sought from the primary or secondary caregiver and assent was sought from children 7-16 years of age using written consent forms (Appendix 11). Data collectors read out and explained the information on the consent form to the caregiver and also to the child as applicable.

Following the consent process, each child recruited into the study was issued with a study ID number which was linked to the child's clinic ID (OI/ART Number) and to the child's name through a separate list that was available only to the research team.

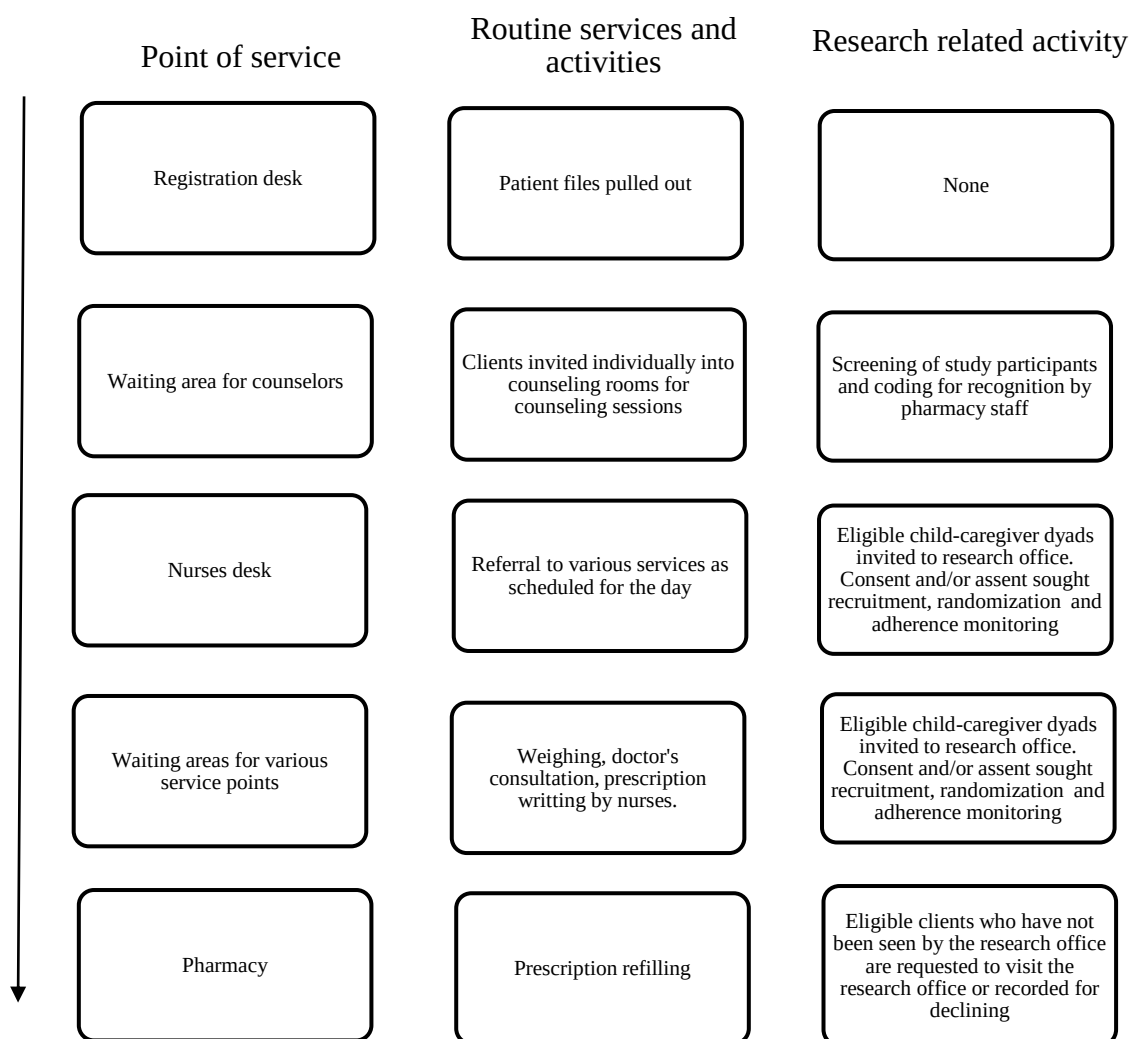


Figure 5 3: Flow chart of patient services and data collection activities

5.12.5 Randomization

After obtaining signed consent from both the guardian caregiver and the child, study participants were randomized into two groups of approximately the same size; the experimental group for adherence monitoring by the ‘new 10-day tool’ and the control group for adherence monitoring by the ‘PACTG-style tool’. Randomization was done using computer-generated random numbers from an online research randomizer downloaded from <http://www.randomizer.org/form.html>

Since neither of the two adherence monitoring tools was routinely applied to monitor adherence in these settings, the participants and the service providers were not aware to which group (control or experimental) the child-caregiver dyads had been randomized. As the interviewer automatically knew which tool was being applied to each individual, the trial employed a single-blinding design. Randomization was applied at this point to minimize the effects of non-response bias on the characteristics of the two randomization groups. The list of randomized numbers was kept in a central place and each interviewer would use the next random number in the row of randomized numbers, with an even number representing allocation to the experimental group and an odd number to the control group.

One factor was considered for stratified randomization using computer-generated random numbers; age of child ≥ 10 years or age of child below 10 years. As adherence was going to be assessed by child reports only in children ≥ 10 years of age, it was necessary to consider this factor in randomization to ensure we had adequate numbers of children in this age group. With a calculated sample size of 264, each of the four blocks was expected to have 66 participants. The four blocks comprised 1) experimental < 10 years, 2) experimental ≥ 10 years, 3) control < 10 years and 4) control ≥ 10 years.

5.12.6 Interviewing and adherence monitoring

Following randomization, adherence monitoring by specified methods was then conducted for each of the two randomized groups. A data collector interviewed and administered a semi-structured questionnaire to caregivers of children on ART recruited into this study. Information collected on the questionnaire was used to describe the programme and to identify factors associated with non-adherence and hence aspects that can be targeted for interventions to improve adherence in settings similar to my study.

Reported adherence using the experimental and the control tools was assessed in children ≥ 10 years of age and to all caregivers of children recruited into the study. The 'PACTG-style tool' was used in the control group for Day 1, Day 2, Day 3, past 7, 14 and 30 days recall of adherence for each ARV in the regimen. Similarly the 'new 10-day tool' was administered to both children ≥ 10 years of age and all caregivers in the experimental group to assess 'past 10 days' adherence. Children ≥ 10 years of age who had a disability that could make it difficult for them to be assessed using these adherence monitoring tools were exempted from

adherence monitoring by child reports. The MMAS-8 was used across all study groups as a second measure of adherence by caregiver reports only.

5.12.7 CD4 measurements and medical history

Clinical records of children recruited to the study were reviewed to collect data on CD4 measurements in addition to other medical history.

5.12.8 Focus group discussions

FGDs were conducted to obtain insight into the underpinnings of adherence behaviour and reporting of non-adherence (Folch-Lyon, Trost 1981), Conducting focus group sessions) through an open conversation environment to allow participants to comment and ask questions or respond to questions by the moderator or comments by other participants. This method of data collection, which is a form of group interview, capitalises on group interactions to gain insight and understanding as to how and why children and caregivers think and act the way they do with regard to adherence and reporting non-adherence (Rabiee 2004, Morgan 1996). The time efficient method was employed to allow group interactions to elicit rich and more sensitive data and to collect high quality data (Lederman 1990) regarding experiences of taking ARV medication, challenges to adherence and challenges in reporting non-adherence. A focussed interview guide (Lederman 1990) was developed, being informed by Morrison-Beedy, Côté-Arsenault and Feinstein (2001), and was used to guide discussions and to ensure inclusion of all relevant issues to be covered during the FGDs (Appendix 12).

5.12.8.1 Aim of the FGDs

The aim of FGD component of the study was to establish how non-adherence occurs and identify challenges to adherence and barriers to reporting adherence accurately.

5.12.8.2 Composition of focus groups

Five FGDs were conducted; three with caregivers of children on ART and two with children 13 to <16 years of age who were on ART to discuss challenges to ART adherence in children. The minimum age for the child FGD participants was raised to 13 years so as to narrow the age range within the group hence promoting homogeneity within each group (Large, Beheshti 2001). Two FGDs, one for adults and one for children were conducted at the Murambinda Mission Hospital whilst the rest were conducted at Harare Children's Hospital.

Each caregiver group comprised at least one caregiver who was not a biological parent to the child, one caregiver to a biological child and one caregiver who was also on ART. Similarly the groups of children on ART also included at least one child cared for by a biological parent, one child cared for by a non-biological parent and one child whose caregiver was taking ART. Based on findings from the literature (McLafferty 2004) a minimum of five participants was required for each FGD and up to 8 participants in a group was considered a large enough number to trigger a sufficiently active dialogue and yet allow all participants to have a chance to present their point of view.

5.12.8.3 Selection of FGD participants

The FGDs were conducted on the same day as the interviews. Child and caregiver FGD participants were identified during interviews with caregivers and needed to be strangers to each other outside the hospital setting to allow for frank talk during discussions. FGDs were conducted on those days when an adequate number of participants was available for this process.

5.12.8.4 Conducting the FGDs

The principal researcher, who is experienced in moderating FGDs and is a native Shona speaker, was the moderator for all FGDs whilst two data collectors acted as assistant moderators. The moderator's role was to guide the discussion, keep conversation flowing, observe non-verbal communication and, rarely, take notes on very important observations. The roles of the assistant moderators were to take notes, operate the recorder, handle the environment (such as responding to unexpected interruptions) and keep track of time for the breaks and completion of the discussion. Discussions were guided by an FGD guide (Appendix 12a and 12b) and discussions were recorded with an Olympus® voice recorder.

As each member entered the discussion room, the note taker took details of the participants and asked the participants to indicate to the moderator in privacy if there was anybody in the room whom they knew personally from outside the hospital setting. At the start of the discussion, the moderator welcomed the group members and introduced the research team. Participants were asked to introduce themselves by the names they preferred group members to call them. The moderator and the note taker checked if any of the members knew each other outside the clinic and FGD setting so as to avoid such situations. They also stressed issues of confidentiality of information by the researchers and group members and pointed to

the fact that all contributions by any group member were valuable for the research. Members were reaffirmed that there were no right or wrong answers and that all should feel free to contribute their experiences and thoughts on the discussion topics and any other related issues. Permission to record the discussions was requested and obtained from all participants. Consent to participate in the FGDs was included in the main consent form (Appendix 11)

The moderator ensured that all topics listed on the discussion guide were covered, although a strict sequence of topics was not adhered to. Any unexpected issues that arose relevant to adherence to ART in children and to reporting of adherence were followed up by the moderator to allow adequate discussion on these in addition to those listed in the FGD guide. During the discussions the moderator would guard against detours but would allow flexibility in the discussions to elicit serendipitous but relevant information (Morrison-Beedy, Côté-Arsenault & Feinstein 2001). The moderator avoided the approach of actively leading the group to facilitate an environment of equality with the participants although this was more difficult with child groups. Discussions with children lasted about 45 minutes to an hour and with caregiver lasted about an hour to an hour and 30 minutes.

Additional to the small stipends, FGD participants were served with refreshments at breaks between the discussions.

5.12.8.5 Analysis of FGD data

Analysis of the FGD data was guided by the ‘framework analysis’ described by Rabiee (2004). During the discussions the moderator, who is the principal researcher and a native of the language used in the discussions, took note of hesitations, laughter, unison responses, enthusiasm and other nonverbal communication indicators. After the discussion, the moderator listened to the tapes several times and brought these nonverbal indicators into the context of the discussion during transcription. The transcriptions prepared by the principal researcher were translated into English and typed onto Microsoft[®] Excel sheets by two social science graduates who are natives of the language used by participants but have had all their education up to the degree level in English.

Based on the ‘framework analysis’ described by Rabiee (2004) the thematic approach was used with themes being developed from both the research questions as per FGD guide (Appendix 12) and from participant dialogue. The principal researcher went through the

tapes, the translated transcripts and field notes several times to familiarise herself with the information and develop detailed insight into the discussion content. The two social science graduates, who have experience in analysing data collected through FGDs, went through the transcripts writing short phrases, ideas and concepts into adjacent columns of the Excel sheets based on participant statements in the transcripts and based on the discussion climate described therein from the notes. These ideas and concepts were colour coded. Two sets of the colour coded Excel sheets were printed. From one set, cut-outs of the colour coded information were made and these were posted onto segments of manila sheets arranging them by colour (themes) and by the focus group from which they were extracted. The categorisation of information by source group allowed the analysis team to examine patterns of the occurrence of concepts and ideas and to analyse inter- and intra-group information (Folch-Lyon, Trost 1981). Specific comparisons in coding were also made between adults and children (Fetzer et al. 2011). Findings and relevant quotations were organised by topics and themes and were consolidated into a final report (Ngarina et al. 2013).

5.13 Sample size

Based on the information presented in a South African study (Müller et al. 2008), it was assumed that 91% of the children would be >95% adherent by caregiver reports using current self-report adherence monitoring methods such as the ‘PACTG-style tool’, and that the ‘new 10-day tool’ will produce non-adherence levels that are not as high as those produced by MEMS[®] but are at least 25% better than current self-reports in detecting non-adherence. In the Müller’s study (Müller et al. 2008), 91% of children were >95% adherent using caregiver reports compared to only 36% by MEMS[®]. Considering that in this study a new self-reported adherence monitoring tool was being assessed using an existing ‘PACTG-style tool’ as a control, it was considered unlikely that the ‘new 10-day tool’ would be as good as MEMS[®] in detecting non-adherence. For this reason it was considered that targeting adherence levels that are approximately midway between current self-reports and MEMS[®] would be practically reasonable. This resulted in the prediction of a 25% decrease in the number of children detected to be adherent by the ‘new 10-day tool’ below those detected by the existing ‘PACTG-style tool’.

With these assumptions, a minimum sample size of 60 children in each of the control and experimental groups was calculated for the study to have 80% power for the detection of a

difference of at least 25% in the proportion of children taking at least 95% of their prescribed medication at 5% level of significance. Considering that adherence levels as reported by children ≥ 10 years would be used for the comparison between the experimental and the control groups, the minimum sample size would be applicable to this group as well. With the randomization stratified by age of < 10 years and ≥ 10 years, the sample size in one arm was doubled to 120 giving equal numbers between the age groups. An anticipated dropout rate of 10% gave an adjusted sample size of 132 in each group and a total sample size of 264 for combined groups.

The theoretical basis for calculating the sample size for this RCT was that presented in the following formula for calculating sample size in a superiority study for binary outcomes (Christensen 2007, Wittes 2002)

$$N = (Z_{2\alpha} + Z_{\beta})^2 \times S^2 / \Delta^2$$

N = sample size in one arm

2α = two tailed type 1 error, which was set at 5% (2 tailed significance level = $1 - 2\alpha = 95\%$)

β = type two error risk which was set at 20% (Power = $1 - \beta = 80\%$)

S^2 = variance

Δ = least relevant difference which was set at 20%

Since I was comparing proportions in this RCT, the following formula applies for the variance (S^2) of the difference:

$$S^2 = p1(1-p1) + p2(1-p2)$$

$p1$ (the proportion of adherent children using conventional self-report methods) = 0.91 based on the South African study (Müller et al. 2008)

$p2$ (the anticipated proportion of non-adherent children using the 'new 10-day tool') = 0.66, which is 25% less than $p1$.

2α was set at 0.05 hence $Z_{2\alpha} = 1.96$

β was set at 0.20 hence $Z_{\beta} = 0.84$.

A second sample size large enough to identify factors associated with non-adherence was calculated. Since children depend on their caregiver in taking ARVs, we chose the nature of the caregiver (biological or non-biological) as an important factor that potentially affects adherence to ART (Marhefka et al. 2006a). In a study that was conducted on adherence to ART in Togo (Polisset et al. 2009), it was found that 23 (53.5%) of the children who had one of the parents as their caregiver were adherent and yet only eight (25.8%) of the children who had other than a parent as caregiver were adherent to ART. Based on this information, a sample size of 55 children in each group was calculated to have the power at the 5%

significance level to detect a significant difference in adherent populations between those who had a biological parent as a caregiver and those who did not. Again, since child-reported adherence levels by children ≥ 10 years were also going to be used to identify factors associated with non-adherence for both the 'new 10-day tool' and the 'PACTG-style tool', the minimum sample size of 55 in each randomization group also applied to this age group for each tool. Doubling up this number to include children below the age of 10 years gave a sample size of 110 for each of the two adherence monitoring tools, an overall sample size of 220 and an adjusted sample size of 242 after including a 10% allowance for attrition.

In this study the larger of the two sample sizes i.e. 264 children was therefore used since this figure also met the conditions for identifying factors associated with adherence in the two arms. The sample size for the RCT was calculated manually and the second sample size for identifying factors associated with non-adherence was calculated using Epi InfoTM version 6 Statcalc programme.

5.14 Data analysis

Quantitative data were analysed using Epi InfoTM and SPSS software. The level of significance was set at $P < 0.05$ for a two-tailed test.

5.14.1 Characteristics of study participants

Student's t-test and the Mann-Whitney U test for means, and chi-square tests and the Fishers exact test were used to evaluate the effectiveness of the randomization process by comparing the two randomized groups.

5.14.2 Establishing levels of adherence to ART in children

Adherence levels were calculated as a proportion of prescribed doses that were taken by the child. Adherence levels were dichotomized as appropriate when feasible, using three adherence thresholds: taking at least 80% of all prescribed doses which has been found to be significantly associated with virological response (Farley et al. 2003a, Mills et al. 2006), taking at least 95% of all prescribed doses which has been found to result in optimal benefits from ART (Elise et al. 2005) and taking 100% of all prescribed doses which is desirable for any treatment.

Only the 100% adherence threshold was used for Day 1, Day 2, and Day 3 self-reported adherence by the 'new 10-day tool' and the control 'PACTG-style tool'. For 'past 7 days' reported adherence, both the 100% and 80% adherence thresholds were used. Finally, all three adherence thresholds were used for reported adherence for 'past 10 days', 'past 14 days' and 'past 30 days'.

Combined experimental and control group self-reported adherence levels were computed for Day 1, Day 2, Day 3 and 'past 7 days'. 'Past 10 days' self-reported adherence levels were determined only for experimental group whilst 'past 14' and 30 days adherence levels were computed only for the control group based on the design of the tool.

Following dichotomization of adherence levels, study participants were then classified as adherent or non-adherent based on the above cut-off points with subsequent calculation of proportions of children that are adherent. The proportions were converted into percentages for ease of interpretation.

Self-reported adherence by the 'new 10-day tool' and its comparator was always treated as a dichotomous variable. Self-reports at 100% cut-off point were mainly used for some validity testing other than the superiority test since self-reports yield high adherence levels (Jaspan et al. 2011) and have high sensitivity and low specificity and, whilst sensitivity remained constant at different adherence cut off points, specificity improved at higher adherence cut-off points (Müller et al. 2011).

Adherence by the MMAS-8 was classified into High (score = 8), Intermediate (score = 6-7) and Low (score <6) and median scores were also calculated. MMAS-8 scores were treated as a continuous variable for comparison with self-reports and as a dichotomous variable in comparison with pill counts.

Pill count adherence was mainly used as continuous variable but was also dichotomised for comparison between the two pill count methods and between the two randomisation groups whilst discrepancy in pill counts was used only as a continuous variable.

5.14.3 Association between constructs of theoretical models and adherence

Scores on all items of each construct of theoretical model, (i.e beliefs about medicines, self-efficacy, social support and external factors) were summed to obtain a total (sum) score. Spearman correlation coefficient (Spearman's ρ), and Kendall's tau-b correlation coefficient for $n < 20$, were used to determine the relationship between adherence levels by the different methods and sum scores of each theoretical model.

5.14.4 Validity and reliability testing of the tool

A validation of the new self-report tool was conducted using adherence data from other adherence monitoring methods as well as from adaptations of validated constructs of behaviour change models such as self-efficacy and beliefs about medicines scales and social support.

5.14.4.1 Superiority test

Superiority test of the 'new 10-day tool' was based on the assumption that self-reports have low specificity but extremely high sensitivity for adherence. Based on previous studies (Deschamps et al. 2008, Jasti et al. 2006, Kouanfack et al. 2008), Müller et al. 2011, Nabukeera-Barungi et al. 2007) the differences in reported adherence between the 'new 10-day tool' and its comparator ('PACTG-style tool') would be attributed mainly to either decreased or increased specificity as opposed to differences in sensitivity for adherence behaviour. Comparison of the adherence levels between the two methods using the RCT (Mannheimer et al. 2008) would give an indication of which of these is more specific for adherence (i.e having lower adherence level that reflect the detection of more non-adherent cases as opposed to missing out adherent cases).

Based on this assumption, adherent proportions between the 'new 10-day tool' and the experimental 'PACTG-style tool' were compared and significance in the differences between adherent proportions was tested using 95% confidence intervals.

To avoid bias introduced by the adherence assessment recall periods (Lu et al. 2008), the superiority test between the experimental 'new 10-day tool' and the control PACTG-style tool was done on similar or close adherence assessment recall periods, of Day 1 to Day 3 and 'past 7 days' and for 'past 10 days' in the experimental group compared to 'past 14 days' in

the control group. For the rest of the evaluations, comparison was made for the ‘past 7 days’, which is the longest period that is common to both tools, and at the 100% level due to the extremely high adherent proportions that is characteristic of reported adherence (Davies et al. 2008, LePrevost et al. 2006, Mannheimer et al. 2008) and lower specificity (Müller et al. 2011) that are obtained with self-reports at lower adherence cut-off points. Additional to this, comparisons were also made for the maximum periods in each tool; 10 days in the experimental tool and 30 days in the control tool.

5.14.4.2 Concurrent validity

Concurrent validity (a type of criterion validity) of the ‘new 10-day tool’ at 100% adherence cut-off point was evaluated through the nature of the relationship between ‘past 7 days’ and ‘past 10 days’ reported adherence measured by the ‘new-10 day’ tool, and that measured by the MMAS-8 using the Mann-Whitney U test. The same evaluation was conducted for the ‘PACTG-style tool’ for ‘past 7 days’ and ‘past 30 days’ adherence at 100% cut-off point for comparison.

5.14.4.3 Reliability

Inter-rater reliability analysis (Vitolins et al. 2000, Landis, Koch 1977, Viera, Garrett 2005) of both the ‘new 10-day tool’ and the ‘PACTG-style tool’ for comparison was conducted through the level of agreement between the adherence reports of the child and that of his/her caregiver as measured by the same tool, and assessed using the kappa statistic with interpretation of kappa values being based on a classification recommended by Landis and Koch (1977) as follows:

<0 - Poor agreement

0-0.20 - Slight agreement

0.21 to 0.40 - Fair agreement

0.41 to 0.60 - Moderate agreement

0.61 to 0.80 - Substantial agreement

0.81 to 1.00 - Almost perfect agreement

Association between the ‘new 10-day tool’ and constructs of theoretical models was assessed by comparing mean scores on self-efficacy, beliefs about medicines, perceived social support

and ‘external’ factors, between adherent and non-adherent children, using the Mann-Whitney U test with a similar test being conducted on the control tool.

5.14.5 Factors associated with adherence

Test of associations between child and caregiver-reported adherence and, socio-demographic and socio-economic characteristic as well as clinical and ART-related care factors, was conducted firstly in univariate analysis followed by multiple logistic regression models including all factors associated at 10% significance level.

5.14.6 Assessment of two pill count methods

The two pill count methods, a routinely-used method and one that incorporated the reported residual quantity (RRQ) of medication at last refill (‘Pill count RRQ’), were assessed for feasibility and compared using proportions adherent at all three adherence cut-off points, 80%, 95% and a100%, and 95% CI, Correlations with self-reported adherence were conducted to determine which of the two pill count methods used in this study had a better overall estimate of adherence.

CHAPTER 6: RESULTS

6.1 Introduction

This chapter presents findings from a superiority RCT that was used to evaluate a ‘new 10-day tool’ for monitoring adherence in children on ART using a ‘PACTG-style tool’, a slightly modified version of the PACTG Adherence tool module 1-III (Steele, Grauer 2003, Davies et al. 2008, Chesney et al. 2000, Davies et al. 2011), as a control, in caregivers and children ≥ 10 years of age. The MMAS-8 (Morisky et al. 2008) was used to measure caregiver-reported adherence in both the experimental and control groups for the purposes of concurrent validation of the ‘new 10-day tool’. Adherence levels for the experimental ‘new 10-day tool’, the control ‘PACTG-style tool’ and the MMAS-8 are presented. Inter-rater reliability (Vitolins et al. 2000, Landis, Koch 1977) of the ‘new 10-day tool’ was assessed through the test of agreement on adherence levels between child-caregiver pairs. Findings on the validity and reliability of the ‘new 10-day tool’ are presented and factors associated with reported adherence are identified.

In addition, results of the assessment of the feasibility of using pill count method for routine monitoring of adherence in my study settings are presented in the form of adherence levels measured by two pill count methods. The use of caregiver reports on residual quantity of pills at the last refill, to improve the accuracy of the pill count method, is explored. The percent discrepancy in pills returned to the clinic on a review and refill visit is assessed as a measure of both adherence and medication-handling behaviour.

6.2 Screening, recruitment and randomization

Seven hundred children under the age of 16 years coming for review of ART and refill of ARVs, and their accompanying caregivers, were screened for eligibility to enter into the study in November and December 2009, as shown in Figure 6.1. Recruitment and data collection continued for a month at each site. Just above half (51.7%; $n = 362$) of the total child-caregiver pairs screened were excluded for not meeting the inclusion criteria; 205 of the children had caregivers coming to collect medicines without the child, 106 were children coming to collect medicines unaccompanied by either a primary or a secondary caregiver, 34 were brought by caregivers who had not been staying in the same household as the child 30 days prior to the study, eight were the second child brought by the same caregiver and seven

were among the 10 who had participated in the pilot study. The majority of those who did not meet the inclusion criteria were children 10 years of age and above (65.0%; n = 235).

Of the 338 child-caregiver pairs who met the inclusion criteria, 74 (21.9%) could not be located after screening. This was mainly because screening was done after registration for the day's services but before receiving routine clinical services for the day, whilst interviews were conducted when participants were waiting for their turn to be served or after receiving the clinical services due for them on the visit. Those who were loss to follow-up would leave the clinic without getting to the data collection point.

Consent and assent, as appropriate, was sought from 264 child-caregiver pairs and of these, 18 caregivers from the urban site declined to participate, giving an overall decline rate of 6.8%. The main reason for caregivers declining to participate in the study was that they were late for their next appointment and could not spare time for the interviews and adherence monitoring (16 out of 18). One caregiver declined because she needed permission from the father, who was not available, and another caregiver did not give any reason for declining to participate in the study. No child declined to participate in the study.

The ultimate number of child-caregiver pairs recruited into the study was 246, with 123 in the experimental arm and 123 in the control arm. One child in the control arm could not be included in analysis because the data collection process was disrupted at its start when the child fell and was crying, and as a result the caregiver decided to terminate the interview. As can be seen in Table 6.1 below, the attrition rate following screening was higher at the urban Harare Children's Hospital, than at the rural Murambinda Mission Hospital.

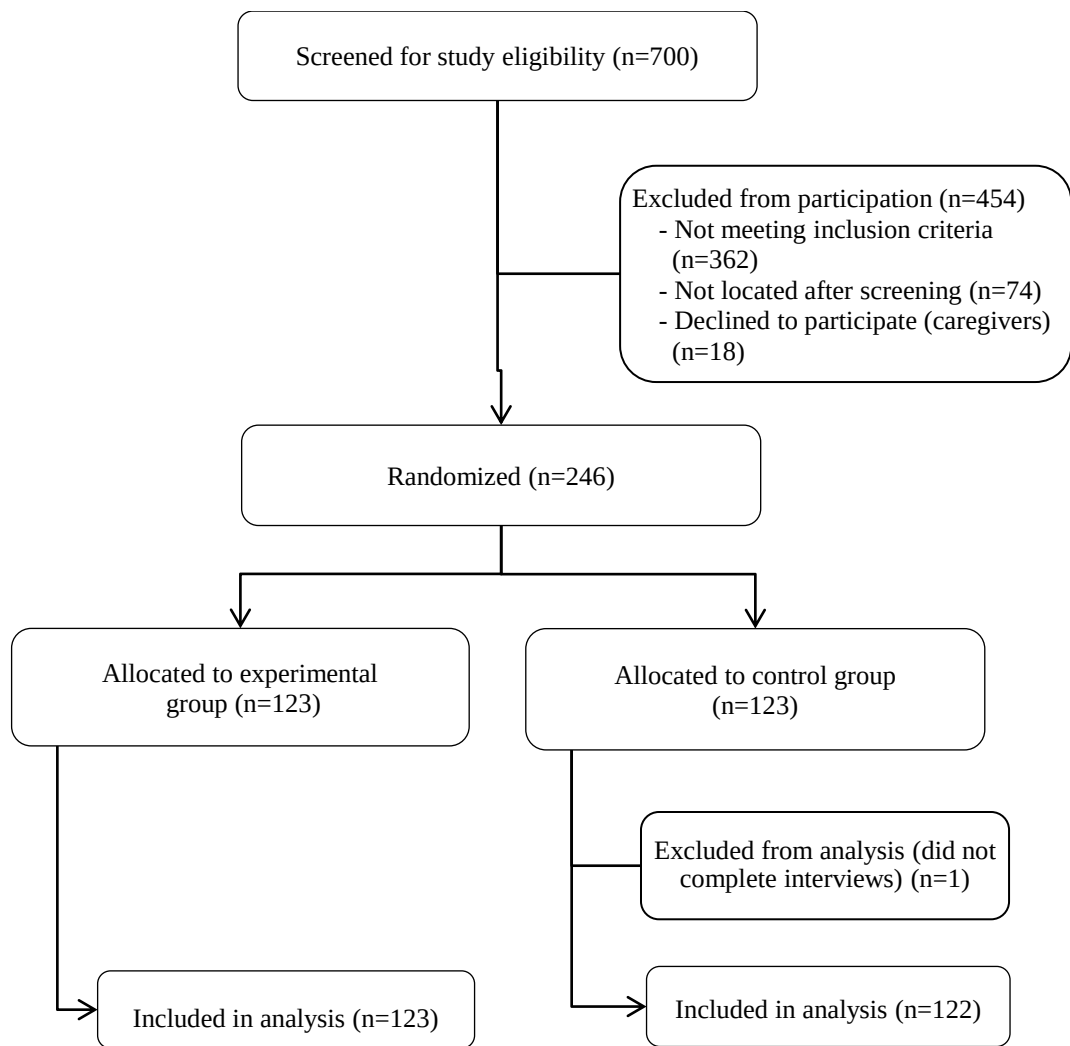


Figure 6.1: CONSORT diagram for the randomized control trial

Table 6.1: Number of child-caregiver pairs screened and recruited by study site

	Urban Harare Children's Hospital n (%)^a	Rural Murambinda Mission Hospital n (%)^a	Total n
Screened	514 (73.4)	186 (26.6)	700
Ineligible	297 (82.0)	65 (18.0)	362
Eligible	217 (64.2)	121 (35.8)	338
Could not be located after screening	66 (89.2)	8 (10.8)	74
Declined to participate in the study	18 (100)	0 (0)	18
Consented	133 (54.1)	113 (45.9)	246
Recruited and randomised	133 (54.1)	113 (45.9)	246
Included in analysis	132 (53.9) ^b	113 (46.1)	245

^aThese are percentages across sites.

^bOne child fell at the start of the interview so the interview was discontinued and was excluded from analysis.

6.3 Characteristics of study sample

Data were analysed for 245 child-caregiver pairs whose caregivers completed interviews from the two data collection study sites. The majority (91.8%; n = 225) of the 245 caregiver respondents were primary caregivers whilst the remainder were secondary caregivers. The average time taken for the interviews was 37 minutes. Table 6.2 below presents socio-demographic characteristics and Table 6.3 presents clinical and medication information, of child study participants. Table 6.4 presents socio-demographic characteristics of primary caregiver and secondary caregiver as well as health and ART-related care information. To test randomisation, p-values for differences in these characteristics between the experimental and control groups are presented in Tables 6.2 - 6.4.

6.3.1 Socio-demographic characteristics of child and caregivers

The age range of children was from 8 months to 15 years and 11 months with a median of 9 years (Q1, 5yrs and 11 months; Q3, 11 years and 10 months) (Table 6.2). Just above half (52.9%; n = 129) of the children were female and almost all (94.5%; n = 154) of the children above the age of seven years were attending formal school. The majority of the children were in primary school, a level that covers the first seven years of formal education. The highest

school grade among the children was Form 3, a grade which is one year below that of attaining the general certificate of education in Zimbabwe and corresponds to 10 years of formal education. There were no significant differences in characteristics of children between the experimental group and the control group with regard to age, sex, school attendance, type of usual place of residence and orphanhood, as illustrated in Table 6.2.

Table 6.2: Socio-demographic characteristics of study child study sample

Variable	Total ^a	Experimental ^a	Control ^a	P-value
Age of child (yr)				
n	245	123	122	0.893 ^b
Mean ± SD	8.66 ± 3.91	8.69 ± 3.86	8.623 ± 3.97	
Sex, n (%)				
Female	129 (52.9)	66 (53.7)	63 (52.1)	0.803 ^c
Male	115 (47.1)	57 (46.3)	58 (47.9)	
Type of usual residence, n (%)				
Urban	124 (50.6)	66 (53.7)	58 (47.5)	0.338 ^c
Rural	121 (49.4)	57 (46.3)	59 (52.5)	
Attending school, n (%)				
Yes	182 (74.3)	93 (75.6)	89 (73.0)	0.741 ^c
No	63 (25.7)	30 (24.4)	33 (27.0)	
Child's years of formal schooling, n (%)				
None	77 (31.4)	40 (33.1)	37 (30.6)	0.453 ^c
0-7	151 (61.6)	72 (59.5)	79 (65.3)	
8-11	14 (5.7)	9 (7.4)	5 (4.1)	
Lost at least one parent (orphan), n (%)				
Yes	167 (68.2)	79 (64.2)	88 (72.1)	0.234 ^c
No	78 (31.8)	44 (35.8)	34 (27.9)	
Type of orphanhood, n (%)				0.804 ^c
Double	69 (41.3)	31 (39.2)	38 (43.2)	
Paternal	51 (30.5)	26 (32.9)	25 (28.4)	
Maternal	47 (28.5)	22 (27.8)	25 (28.4)	

^aParticipants with missing information are not included.

^bt-test.

^cPearson's Chi-Square test.

6.3.2 Clinical and medication information of child study sample

Information on health and ART characteristics of study participants is reported in Table 6.3. About half of the children had been diagnosed with HIV in the past 1½ - 4 years (median = 33.0 months [Q1, 17; Q3, 48.8]). Again about half of the children had been on treatment for a period of ½ - 3 years (median = 17.5 months [Q1, 6.0; Q3, 34.5]). The median interval between the HIV diagnosis and the initiation of ART was 8 months (Q1, 2; Q3, 18).

Almost all (99.6%; n = 244) of the children were taking first line ARV regimens, with 229 (93.5%) taking stavudine, lamivudine and NVP and 12 (5.0%) taking efavirenz as a substitute to NVP mainly due to co-treatment with anti-TB drugs. Two were on protease inhibitor-based first line regimens containing lopinavir boosted with ritonavir. Only one had been switched to a second line regimen containing didanosine, abacavir and lopinavir boosted with ritonavir as a result of developing resistance to the first line regimen.

As shown in Table 6.2, ARV substitution had taken place in 11 children. Reasons for substituting ARVs were noted in eight of these 11 children and these included starting TB treatment (5 of 8), side effects (1 of 8) and non-availability of the substituted ARV (2 of 8). ARV drug formulations [the type (tablet or suspension), strength or brand] were changed in 28 children mainly because the child was old enough to progress to either the next dosage strength and/or change to solid dosage forms (n = 23). Three children changed ARV formulations in order to reduce the dosages and only one child had changed formulations as a result of unavailability of the medication s/he was taking at that time.

Four children had, at some point, failed to get ARVs from the clinic/hospital where they were receiving ART services. Only one of these four children had his/her medicine bought from the retail pharmacy as a result of this unavailability of the medicine at the health facility. The other three children had to wait for supplies to be available at the ART clinic. However, only one child reported missing doses due to this unavailability of the medicines at the ART clinic. There was no significant difference in health and treatment characteristics between the experimental and control groups except for time when the child was last hospitalised and whether the child was taking cotrimoxazole prophylaxis or not. Fewer controls were taking cotrimoxazole prophylaxis and more controls had been hospitalised before initiating ART, a difference which could probably be due to chance.

Table 6.3: Clinical and medication information of child study sample

Variable				Total ^a	Experimental ^a	Control ^a	P-value
Period since HIV diagnosis (months)							
n				220	109	111	
Median	(Inter-quartile	range		33.0 (17.3, 48.8)	35.0 (18.5, 48.5)	33.0 (15.0-49.0)	0.551 ^b
[Q1,Q3])							
Duration on treatment (months)							
n				221	108	113	
Median (Q1,Q3)				17.5 (6.0, 34.5)	20.0 (1.0, 36.0)	17 (6.0, 31.5)	0.449 ^b
ARV regimen, n (%)							
First line				244 (99.6)	123 (100)	121(99.2)	0.498 ^c
Second line				1 (0.04)	0 (0.0)	1 (0.8)	
Dosage form, n (%)							
Solid				242 (98.8)	121 (98.4)	121 (99.2)	1.00 ^c
Liquid or both				3 (1.2)	2 (1.6)	1 (0.8)	
Number of ART medicines, n (%)							
1				217 (88.6)	112 (91.1)	105 (86.1)	0.235 ^c
2 or 3				28 (11.4)	11 (8.9)	17 (13.9)	
Substituted ARV regimen, n (%)							
Yes				11 (4.5)	6 (4.9)	5 (4.1)	1 ^c
No				234 (95.5)	117 (95.1)	117 (95.9)	
Switched to second line regimen, n (%)							
Yes				1 (0.4)	0 (0.0)	1 (0.8)	0.498 ^c
No				244 (99.6)	123 (100)	121 (99.2)	
Changed ARV formulations, n (%)							
Yes				28 (11.6)	16 (13.3)	12 (9.9)	0.427 ^c
No				214 (88.4)	104 (86.7)	110 (90.1)	
Changed health facility since initiating ART, n (%)							
Yes				13 (5.5)	7 (6.0)	6 (4.9)	0.498 ^c
No				225 (94.5)	109 (94.0)	116 (95.1)	
Failed to get supply of ARVs at any health facility, n (%)							
Yes				5 (2.1)	4 (3.3)	1 (0.8)	0.213 ^c
No				236 (97.9)	116 (96.7)	120 (99.2)	
Ever bought ARVs from retail pharmacy, n (%)							
Yes				1 (0.4)	0 (0.0)	1 (0.8)	1 ^c
No				240 (99.6)	120 (100)	120 (99.2)	
Taking cotrimoxazole prophylaxis							
Yes				228 (93.1)	121 (98.4)	107 (87.7)	0.001c ^d
No				17 (6.9)	2 (1.6)	15 (12.3)	

Variable	Total ^a	Experimental ^a	Control ^a	P-value
On TB treatment				
Yes	10 (4.1)	2 (1.6)	8 (6.6)	0.060 ^c
No	235 (95.9)	121 (98.4)	114 (93.4)	
Ever been hospitalized, n (%)				
Yes	136 (56.7)	62 (51.7)	74 (61.7)	0.152 ^c
No	104 (63.3)	58 (48.3)	46 (38.3)	
Hospitalized more than once, n (%)				
Yes	57 (43.5)	24 (39.3)	33 (47.1)	0.384 ^c
No	74 (56.5)	37 (60.7)	37 (52.9)	
When last hospitalized, n (%)				
Before initiating ART	72 (75.0)	27 (64.3)	45 (83.3)	0.017 ^{ef}
≤6 months after initiating ART	7 (7.3)	3 (7.1)	4 (7.4)	
>6 months after initiating ART	17 (17.7)	12 (28.6)	5 (9.3)	
Baseline CD4% in children <5yrs ^g				
n	28	12	16	
median (Q1, Q3)	12 (7.2, 18.9)	12.5(8.3, 25.1)	11.5 (4.8, 14.8)	
Baseline CD4 count in children ≥5yrs ^g				
n	153	81	72	
median (Q1, Q3)	312 (187, 485)	319 (187, 474)	308 (190, 504)	

^aParticipants with missing information are not included.

^bMann-Whitney U test.

^cFisher's exact test.

^dSignificant at p <0.00.

^eLinear by linear association.

^fSignificant at p <0.05.

In this study we relied on CD4 measurements that were routinely collected for clinical use. It was noted during planning and data collection for this study that, whilst CD4 measurements should be done every 6 months, challenges in availability of this service resulted in irregular CD4 measurement that affected the availability of the results for this study. Only 65.7% (n = 161) had a report on CD4 measurements in their medical files which had been done within seven months prior to recruitment. There was no significant difference in mean baseline CD4% in children younger than 5 years and mean CD4 count in children who were 5 years and older between the experimental group and the control group using the non-parametric Mann-Whitney U test as shown in Table 6.3.

6.3.3 Caregiver characteristics

The age range of the primary caregivers included in analysis was 17 - 82 years and that of the secondary caregivers was 11 - 89 years, with an overwhelming majority of the primary caregivers being female (91.8%; n = 225) compared to just above half (57.6%; n = 99) of the secondary caregivers who were female (Table 6.4). Primary caregivers were less educated (35%; n = 84) than the secondary caregivers (25.3%; n = 41) having only up to seven years of formal education (p = 0.039). There was no significant difference in the mean age of primary caregivers (40.5 ± 13.7 years) and that of secondary caregivers (36.0 ± 18.0 years).

Table 6.4: Caregiver characteristics and caregiving information

Variable	Total ^a	Experimental ^a	Control ^a	P-value
Age of primary caregiver (yr)				
n	234	118	116	0.932 ^b
mean ± SD	40.5 ± 13.7	40.5 ± 12.7	40.6 ± 14.8	
Sex of primary caregiver, n (%)				
Female	225 (91.8)	115 (93.5)	110 (90.2)	0.362 ^c
Male	20 (8.2)	8 (6.5)	12 (9.8)	
Relationship of primary caregiver to child, n (%)				
Biological parent	110 (44.9)	60 (48.8)	50 (41.0)	0.220 ^c
Other	135 (55.1)	63 (51.2)	72 (59.0)	
Years primary caregiver lived with child				
n	243	122	121	0.977 ^b
Mean ± SD	7.4 ± 11.1	8.5 ± 14.9	6.2 ± 4.5	
Marital status of primary caregiver, n (%)				
Never married	20 (8.2)	8 (6.5)	12 (9.8)	0.473 ^c
Married	125 (51.0)	60 (48.8)	65 (53.3)	
Widowed	83 (33.9)	47 (38.2)	36 (29.5)	
Divorced	17 (6.9)	8 (6.5)	9 (7.4)	
Primary caregiver's years of formal schooling, n (%)				
None	10 (4.2)	4 (3.3)	6 (5.0)	0.510 ^c
1-7	74 (30.8)	44 (36.4)	30 (25.2)	
8-9	48 (20.0)	21 (17.4)	27 (22.7)	
10-11	103 (42.9)	50 (41.3)	53 (44.5)	
12-13	5 (2.1)	2 (1.6)	3 (2.5)	
Age of secondary caregiver (yr)				
n	157	84	73	0.124 ^b
mean ± SD	36.0 ± 18.1	33.9 ± 18.1	38.4 ± 17.9	
Sex of secondary caregiver				
Female	99 (57.6)	55 (59.1)	44 (55.7)	0.648 ^c
Male	73 (42.5)	38 (40.9)	35 (44.3)	

Variable	Total ^a	Experimental ^a	Control ^a	P-value
Years living with secondary caregiver				
n	168	89	79	0.793 ^b
mean ± SD	5.9 ± 4.3	5.9 ± 4.3	6.0 ± 4.5	
Years of formal schooling for secondary caregiver, n (%)				
None	9 (5.6)	5 (5.7)	4 (5.4)	0.771 ^c
1-7	32 (19.8)	17 (19.3)	15 (20.3)	
8-9	23 (14.2)	13 (14.8)	10 (13.5)	
10-11	87 (53.7)	45 (51.1)	42 (56.8)	
12-13	11 (6.8)	8 (9.1)	3 (4.1)	
Primary caregiver who ever had an HIV test	181 (80.4)	92 (82.1)	89 (78.8)	0.931 ^c
Primary caregiver reporting to be HIV positive	125 (55.5)	66 (58.9)	59 (52.2)	0.882 ^c
Primary caregiver reporting to be taking chronic medication (both ART and non-ART)	117 (52.0)	59 (52.7)	58 (51.3)	0.886 ^c
Primary caregiver reporting to be on ART	77 (34.2)	40 (35.7)	37 (32.7)	0.810 ^c
Responsibility for taking medication				
primary caregiver alone	80 (32.7)	38 (30.9)	42 (34.4)	0.833
primary caregiver and child jointly	42 (17.1)	22 (17.9)	20 (16.4)	
primary caregiver, child and secondary caregiver jointly	123 (50.2)	63 (51.2)	60 (49.2)	
Disclosure of HIV status to child of any age	110 (45.3)	57 (46.3)	53 (43.4)	0.875 ^c
Disclosure of HIV status to children above the age of 7 years	101 (64.3)	53 (67.1)	48 (60.8)	0.407
Disclosure of HIV status to another person other than primary caregiver	213 (94.7)	105 (93.8)	108 (95.6)	0.977 ^c

^aParticipants with missing information are not included.

^bt-test.

^cPearson's Chi-Square test.

More than three quarters (80.4%, n = 181) of the 225 participant primary caregivers indicated that they had been tested for HIV, with 125 indicating that their HIV test results were positive. One primary caregiver did not know the test results. According to these reports,

therefore, the prevalence of HIV among primary caregivers who had undergone HIV testing was 69.4%. Just above half (52.0%, n = 117) of the 225 participant primary caregivers indicated that they were on chronic medication (ART and non-ART) and 77 (34.2%) were on ART. There were no significant differences in primary and secondary caregiver characteristics between the experimental and control groups (Table 6.4).

6.3.4 Care information

Disclosure of HIV status to the child was reported in close to half (45.3%; n = 110) of the 245 children recruited into the study and in 101 (64.3%) of the children above the age of seven years (an age that correspond to the first grade of formal school) (Table 6.4). The majority (n = 213, 94.7%) of the 225 participant primary caregivers indicated that they had disclosed the child's HIV status to another person apart from healthcare workers, mainly to a close relative. Over two thirds (n = 172, 70.2 %) of the children had more than one caregiver.

No child was reported to be the sole person responsible for medication-taking. Administering medication to the child was the responsibility of either the primary caregiver alone, primary caregiver and child jointly or primary caregiver, child and secondary caregivers jointly. Other than people, the use of alternate reminders to take medication was common, with close to three quarters (74.2%, n = 181) of the participant caregivers reporting that they use non-human reminders such as an alarm clock (n = 75, 30.7%), caregiver's own medication-taking times (n = 26, 10.7%) and meal times (n = 14, 5.7%).

6.4 Self-reported adherence levels

Self-reported adherence using the 'new 10-day tool' in the experimental group and the 'PACTG-style tool' in the control group, stratified by child and caregiver reports, are presented in Table 6.5. Caregiver-reported adherence in both groups which was measured using the MMAS-8 is shown in Table 6.6.

6.4.1 Adherence levels by the experimental 'new 10-day tool' and the control 'PACTG-style tool'

Table 6.5 presents self-reported adherence levels in the experimental and control groups and shows comparisons between child and caregiver reported adherence. Self-reported adherence levels were very high in both the experimental and control groups. In the experimental group,

percentages of children adherent by caregiver and child reports ranged from 94.3% - 98.4% and 78.4% - 96.1%, respectively, varying by the adherence cut-off point and measurement period. Similarly in the control group percentages of children adherent by caregiver and child reports ranged from 89.2% - 97.5% and 71.2% - 98.1%, respectively. In both groups, lowest adherence levels were observed at the longest adherence measurement period and at highest adherence cut-off point (taking 100% of doses).

Significant differences between caregiver- and child-reported adherences were observed only at the 100% adherence cut-off points for adherence assessment periods of 'past 10 days', 14 days and 30 days. There were no significant differences in reported 100% adherence between children and caregivers over shorter adherence assessment periods of up to 'past 7 days'. At lower adherence cut-off points (taking at least 95% and at least 80% of prescribed doses) there were no significant differences in adherence levels between caregiver and child reports, regardless of the period over which adherence was assessed.

Table 6.5: Adherence levels at the three adherence cut-off points stratified by child and caregiver reports in the experimental ('new 10-day tool') and control ('PACTG-style tool') groups at the various periods of assessment

	Adherence cut-off point (%) doses taken)	Period of assessment (days)	Caregiver ^a n = 122 n (%)	Child ^a n = 51 n (%)	Point estimate ^b	95% CI	P-value
^e Exp.	100%	Day 1	118 (96.7)	48 (94.1)	-2.6	-9.8 to 4.61	0.489
	100%	Day 2	120 (98.4)	48 (94.1)	-4.3	-11.1 to 2.5	0.201
	100%	Day 3	118 (96.7)	47 (92.2)	-4.5	-12.5 to 3.5	0.271
	100%	'past 7 days'	115 (94.3)	43 (84.3)	-1.0	-20.8 to 0.8	0.068
	100%	'past 10 days'	115 (94.3)	40 (78.4)	-15.9	-27.9 to -3.9	0.009 ^c
	≥95%	'past 10 days'	117 (95.9)	45 (88.2)	-7.7	-17.2 to 1.8	0.111
	≥80%	'past 7 days'	118 (96.7)	49 (96.1)	-0.6	-6.8 to 5.6	0.857
	≥80%	'past 10 days'	120 (98.4)	48 (94.1)	-4.3	-11.1 to 2.5	0.201
^f Cntl.	100%	Day 1	116 (96.7)	49 (94.2)	-2.5	-9.6 to 4.6	0.500
	100%	Day 2	116 (96.7)	49 (94.2)	-2.5	-9.6 to 4.6	0.500
	100%	Day 3	116 (96.7)	49 (94.2)	-2.5	-9.6 to 4.6	0.500
	100%	'past 7 days'	114 (95.0)	44 (84.6)	-10.4	-21.0 to 0.2	0.053
	100%	'past 14 days'	112 (93.3)	42 (80.8)	-12.5	-24.1 to -0.9	0.036 ^d
	100%	'past 30 days'	107 (89.2)	37 (71.2)	-1.8	-31.5 to -4.5	0.010 ^c
	≥95%	'past 14 days'	115 (95.8)	49 (94.2)	-1.6	-8.9 to 5.7	0.682
	≥95%	'past 30 days'	115 (95.8)	49 (94.2)	-1.6	-8.9 to 5.7	0.682
	≥80%	'past 7 days'	116 (96.7)	50 (96.2)	-0.5	-6.6 to 5.6	0.878
	≥80%	'past 14 days'	116 (96.7)	50 (96.2)	-0.5	-6.6 to 5.6	0.878
	≥80%	'past 30 days'	117 (97.5)	51 (98.1)	0.6	-4.0 to 5.2	0.818

^aParticipants with missing information are not included.

^bPoint estimate of the difference in percentages of adherent children between child and caregiver reports.

^cSignificant at p <0.01.

^dSignificant at p <0.05.

^eExperimental results using the 'new 10-day tool'.

^fControl results using the 'PACTG-style tool'.

6.4.2 Adherence levels measured by the MMAS-8

Each of the eight items on the MMAS-8 has a score of one with the possible total score ranging from zero to eight. The median sum of scores for all study participants was 8 (Q1, 7;

Q3, 8) with a score range of 3-8. The median in the experimental group was 8 (Q1, 7; Q3, 8) (mean, 7.6 ± 0.8) and in the control group was 8 (Q1, 7; Q3, 8) (mean, 7.5 ± 1.0).

Adherence measured by the MMAS-8 was further classified into three categories (Morisky et al. 2008) as shown in Table 6.6. More than two thirds of the caregivers reported high (perfect) adherence levels by the MMAS-8 score and very few reported low adherence. After collating the low and intermediate categories of adherence levels into one in order to increase sample sizes in each cell category, there was no significant difference in those with high adherence levels and those with low to medium adherence levels between the experimental group and the control group using Pearson's Chi-Square test ($p = 0.877$).

Table 6.6: Adherence levels measured by the MMAS-8

Adherence level (MMAS-8 Score)	Total ^a n (%)	Experimental ^a n (%)	Control ^a n (%)
High (8)	167 (69.9)	83 (70.3)	84 (69.4)
Intermediate (6-7)	63 (26.4)	32 (27.1)	31(25.6)
Low (<6)	9 (3.7)	3 (2.5)	12 (5.0)

^aParticipants with non-responses to one or more items on the MMAS-8 are not included.

6.5 Evaluation of the 'new 10-day tool'

As described in the methodology, evaluation of the 'new 10-day tool' was conducted using a superiority RCT design using the 'PACTG-style tool' as a control to establish if the new tool would detect more non-adherent cases than its comparator, based on the assumption that self-report tools have close to 100% sensitivity but very low specificity for adherence behaviour. Concurrent validity using the MMAS-8 was conducted. Inter-rater reliability of the 'new 10-day tool' was assessed using children and caregiver reports.

6.5.1 Superiority test

Using 95% CI of the difference in adherent proportions between the experimental and the control tools, it could not be demonstrated that the 'new 10-day tool' is superior to its comparator (control), the 'PACTG-style tool', in detecting non-adherence among children on ART in my study setting, since there were no significant differences in caregiver- and child-reported adherence levels between the experimental and the control groups across all

adherence cut-off points of 80%, 95% and 100%, and across the compared adherence assessment periods at Day 1, Day 2, Day 3, ‘past 7 days’ and ‘past 10 days’ (‘new 10-day tool’) and ‘past 14 days’ (‘PACTG-style tool’) as demonstrated in Table 6.7. This analysis is based on the assumption that any differences in adherence measured by the two self-report tools would mainly be attributed to differences in specificity for adherence, resulting in a difference in non-adherent cases being identified.

Table 6.7: Comparison of self-reported adherence levels between the experimental ‘new 10-day tool’ and the control ‘PACTG-style tool’

	Adherence cut-off point	Period of assessment	Experimental ^a Frequency (%)	Control ^a Frequency (%)	Point estimate ^b	95% CI	
Child reports							
	100%	Day 1	48 (94.1)	49 (94.2)	-0.001	-0.0917	0.0897
	100%	Day 2	48 (94.1)	49 (94.2)	-0.001	-0.0917	0.0897
	100%	Day 3	47 (92.2)	49 (94.2)	-0.020	-0.1172	0.0772
	100%	‘Past 7 days’	43 (84.3)	44 (84.6)	-0.003	-0.1430	0.1370
	≤80%	‘Past 7 days’	49 (96.1)	50 (96.2)	-0.001	-0.0750	0.0730
	100%	‘Past 10/14 days’	40 (78.4)	42 (80.8)	-0.024	-0.1796	0.1316
	≤95%	‘Past 10/14 days’	45 (88.2)	49 (94.2)	-0.060	-0.1690	0.0490
	≤80%	‘Past 10/14 days’	48 (94.1)	50 (96.2)	-0.021	-0.1037	0.0617
Caregiver reports							
	100%	Day 1	118 (96.7)	116 (96.7)	0	-0.0450	0.0450
	100%	Day 2	120 (98.4)	116 (96.7)	0.017	-0.0217	0.0557
	100%	Day 3	118 (96.7)	116 (96.7)	0	-0.0450	0.0450
	100%	‘Past 7 days’	115 (94.3)	114 (95.0)	0.007	-0.0636	0.0496
	≤80%	‘Past 7 days’	115 (94.3)	112 (93.3)	0.010	-0.0508	0.0708
	100%	‘Past 10/14 days’	117 (95.9)	115 (95.8)	0.001	-0.0494	0.0514
	≤95%	‘Past 10/14 days’	118 (96.7)	116 (96.7)	0	-0.0450	0.0450
	≤80%	‘Past 10/14 days’	120 (98.4)	116 (96.7)	0.017	-0.0217	0.0557

^aParticipants with missing information are not included.

^bPoint estimate of the difference in percentages of adherent children between child and caregiver reports.

6.5.2 Inter-rater reliability

Inter-rater reliability (Landis, Koch 1977, Viera, Garrett 2005, Vitolins et al. 2000) of the ‘new 10-day tool’, and the ‘PACTG-style tool’ for comparison, was assessed through the level of agreement between the adherence reports of the child and that of his/her caregiver, as measured by the same tool and assessed based on a classification recommended by Landis and Koch (1977). The test of the extent to which the child-caregiver pair reports on taking 100% of prescribed doses were in agreement (i.e. does the specific child report of 100% adherence agree with that of his or her caregiver), using the kappa statistic and its respective z scores, showed that there was significant but moderate agreement between ‘past 7 days’ caregiver and child reports in both the experimental group (kappa; 0.564, $p < 0.001$) and in the control group (kappa; 0.501, $p < 0.001$).

In the experimental group, child-caregiver inter-rater agreement for the ‘past 10 days’ adherence, at the 100% cut-off point, which is the highest period measured by the tool, was also moderate (kappa; 0.407, $p < 0.001$). However for the maximum period of adherence measured by the ‘PACTG-style tool’, which is 30 days, inter-rater agreement between child- and caregiver-reported adherence, at 100% cut-off point, was only fair (kappa; 0.367, $p = 0.001$). This was, regardless of the fact that reported adherence levels by both children and caregivers were both very high across all adherence periods.

6.5.3 Concurrent validity

Concurrent validity (a type of criterion validity) of the ‘new 10-day tool’ at 100% adherence cut-off point was evaluated by conducting a Mann-Whitney U test to evaluate if there was a relationship between mean adherence levels by the MMAS-8 and reported adherence measured by the ‘new 10-day tool’. This test showed that the ‘new 10-day tool’ was valid since there was a significant relationship between adherence levels measured by the ‘new 10-day tool’ and those measured by the MMAS-8. Children who were 100% adherent using the experimental ‘new 10-day tool’ had significantly higher scores on the MMAS-8 than those who were less than 100% adherent using ‘past 7 days’ adherence by both caregiver reports ($p < 0.001$) and child reports ($p = 0.039$) (Table 6.8). Similarly, for ‘past 10 days’ adherence using the ‘new 10-day tool’, scores on the MMAS-8 were higher for children who were reported to be 100% adherent than those who were reported to be less than 100% adherent, by both caregiver reports ($p < 0.001$) and child reports ($p = 0.047$).

Table 6.8: Relationship between reported adherence in the experimental (‘new 10-day tool’) and control (‘PACTG-style tool’) groups and the MMAS-8

	Reporter	Adherence level	n	Scores on MMAS-8			
				Mean Rank	Sum of Ranks	z	P-value ^a
Experimental past 7 days	Caregiver	100%	111	62.69	6958.50	-5.022	<0.001 ^b
		<100%	7	8.93	62.50		
	Child	100%	43	26.99	1160.50	-2.064	0.039 ^c
		<100%	7	16.36	114.50		
‘past 10 days’	Caregiver	100%	111	62.7	6958.5	-5.022	<0.001 ^b
		<100%	7	8.9	62.5		
	Child	100%	39	26.8	1045.0	-1.987	0.047 ^c
		<100%	10	18.0	180.0		
Control ‘past 7 days’	Caregiver	100%	113	61.10	6904.50	-2.982	0.003 ^d
		<100%	5	23.30	116.50		
	Child	100%	43	25.79	1109.00	-0.291	0.771
		<100%	8	27.12	217.00		
‘past 30 days’	Caregiver	100%	107	64.7	6923.0	-5.489	<0.001 ^b
		<100%	12	18.1	217.0		
	Child	100%	37	29.4	1086.5	-2.687	0.007 ^d
		<100%	15	19.4	291.5		

^aMann-Whitney U test.

^bSignificant at P <0.001.

^cSignificant at p <0.05.

^dSignificant at p <0.01.

The same evaluation was conducted for the control tool for comparison using ‘past 7 days’ and ‘past 30 days’ adherence at 100% cut-off point. In the control group, for ‘past 7 days’ adherence at 100% cut off point, only caregiver reports of adherence measured by the ‘PACTG-style tool’ were associated with adherence levels measured by the MMAS-8 (Table 6.8). There were no significant relationships between child-reported adherence levels measured by the ‘PACTG-style tool’ in the control group with those measured by the MMAS-8 for ‘past 7 days’ adherence at 100% cut-off point (Table 6.8). However, for the

'past 30 days' adherence at 100% cut-off point, MMAS-8 scores were higher in adherent groups by both caregiver reports ($p < 0.001$) and child reports ($p = 0.007$)

6.6 Adherence levels measured by clinic-based pill count

Two pill count methods were used, one accounting for the reported amount of medicine the patient had prior to the previous dispensing, and the other assuming that all medication was consumed or collected before reissuing hence disregarding the reports on this excess stock of medicine prior to last dispensing. Respective percent discrepancies in the returned quantity of medicine were calculated for the period between last dispensing and return date. When adherence levels were dichotomised at 80%, 95% and 100% cut-off points, those who appeared to have taken more pills than required were allocated to the adherent group ('capped' adherence).

6.6.1 Availability of pill count data

Using pill count which excludes the residual quantity (RQ) of pills at last refill ('routine pill count'), just above half ($n = 126$; 51.4%) of the 245 child study participants had complete data on all the following four parameters required for computation of adherence levels:

- Quantity dispensed at last refill.
- Quantity returned at current visit.
- Number of tablets to be taken per day.
- Number of days lapsed since last refill.

Close to half ($n = 119$; 48.6%) of the 245 study participants either did not bring in the remaining pills or pill containers on the day they were recruited ($n = 99$; 40.0%) or had missing information for computing the quantity of missed pills such as the date of last refill and/or quantity dispensed at last refill.

The following parameters were required to compute adherence levels measured by pill count using caregiver-reported residual quantity (RRQ) at last refill ('Pill Count RRQ'), to assess the effect of including these patient reports in obtaining more accurate adherence data:

- Quantity of pills dispensed at last refill.
- Reported quantity of pills remaining at last refill (residual quantity at last refill).
- Quantity of pills returned at current visit.

- Number of pills to be taken per day.
- Number of days lapsed since last refill.

Only about a quarter (n = 59; 24.1%) of the 245 child study participants had complete data on all the five parameters needed to compute adherence levels using ‘Pill Count RRQ’. The majority of the study participants either did not bring in the remaining pills with them on the day they were recruited (n = 99; 40.0%), or did not have complete information regarding the residual quantity of pills at last refill, (n = 82; 33.4%). The remainder had other information missing such as the date of last refill or quantity dispensed at last refill.

6.6.2 ‘Capped’ pill count adherence levels in the experimental and control groups

To assess the effect of randomisation into the experimental and control groups on pill count adherence outcomes, we compared the ‘capped’ pill count adherence levels between the two groups (Table 6.9). There was no significant difference in ‘capped’ pill count adherence

Table 6.9: Comparison of ‘capped’ pill count adherence levels between the experimental group and the control group

Adherence measure	Adherence cut-off point	Total ^a	Experimental ^a	Control ^a	Point estimate ^b	95% CI
		Adherent n (%)	Adherent n (%)	Adherent n (%)		
‘Routine pill count’	80%	95 (75.4)	53 (80.3)	42 (70.0)	10.3	-4 to 25
	95%	49 (38.9)	26 (39.4)	23 (38.3)	1.1	-17 to 18
	100%	27 (21.4)	17 (25.8)	10 (16.7)	1.1	-5 to 23
Pill count RRQ	80%	45 (76.3)	22 (78.6)	23 (74.2)	4.4	-17 to 25
	95%	34 (57.6)	20 (71.4)	14 (45.2)	26.2	-1 to 54 ^c
	100%	20 (33.9)	12 (42.9)	8 (25.8)	17.1	-7 to 41

^aParticipants with missing information are not included.

^bPoint estimate of the difference in the two percentages.

^cAsymptomatic, continuity corrected CI.

levels between the experimental and control groups for both ‘Pill count RRQ’ and for ‘routine pill count’ as shown in Table 6.9

6.6.3 ‘Routine pill count’

‘Routine pill count’ adherence levels ranged from -30.0% - 243.7%, with the negative adherence levels being a reflection of patients returning more pills than were dispensed the

previous time and those with adherence levels above 100% reflecting patients returning less pills than were expected for perfect adherence during the adherence assessment period.

Table 6.10: Differences in ‘capped’ adherence levels measured by ‘Pill Count RRQ’ and ‘routine pill count’ in the combined experimental and control groups

Adherence point	cut-off	‘Pill Count RRQ’ ^a n = 59	‘Routine pill count’ ^a n = 126	Point estimate ^b	95% CI
		Frequency (%)	Frequency (%)		
100%		20 (33.9)	27 (21.4)	12.45	-1.6 to 26.9
95%		34 (57.6)	49 (38.9)	18.7	3.3 to 33.0 ^c
80%		45 (76.3)	95 (75.4)	0.9	-13.1 to 13.1
Having more pills than expected for 100% adherence		39 (66.1)	99 (78.6)	-12.5	-29.4 to 4.4
Having less pills than expected for 100% adherence		17 (28.8)	24 (18.3)	10.5	-16.0 to 37.0
Having the number of pills expected when 100% adherent		3 (5.1)	4 (3.2)	1.9	-28.4 to 32.2

^aParticipants with missing information are not included.

^bPoint estimate of the difference in the two percentages.

^cSignificant difference (p <0.05).

6.6.3.1 Percent discrepancy

Just over three quarters of the 126 child study participants who had complete data on pill count returned more pills than expected for 100% adherence, just below a fifth returned fewer pills than expected, and only 3.2% returned the expected number of pills for the visit (Table 6.10). This implies that 124 (96.8%) of the 126 children had a discrepancy of pills using this pill count method.

This discrepancy in pills returned was expressed as a percentage of the total quantity of pills dispensed during this period, regardless of whether it is more pills or fewer pills than expected, to give the percent discrepancy. The mean percent discrepancy for ‘routine pill count’ was 18.7 ± 24.1 , with a range of 0-143.8.

6.6.3.2 ‘Capped’ adherence

Of the 126 children who had complete information on ‘routine pill count’, less than a quarter appeared to be 100% adherent (this included the 18.3% who returned less pills than expected for 100% adherence and hence reflecting adherence levels above 100%), slightly below half were classified as $\geq 95\%$ adherent and just above three quarters were classified as $\geq 80\%$ adherent (Table 6.10). The median adherence level was 91.4% (Q1:80.2%; Q3: 98.3%).

6.6.4 ‘Pill count RRQ’

The range of adherence levels using ‘Pill count RRQ’ was 12.5% - 158.9%. According to ‘Pill count RRQ’, there were no children who appeared to have brought in more pills than those dispensed at the last refill (i.e.no negative adherence levels were observed).

6.6.4.1 Percent discrepancy

Of the 59 child study participants who had complete data for calculation of adherence levels, about two thirds returned more pills than expected for 100% adherence, just below a third returned fewer pills than expected and only 5.1% returned the expected number of pills (Table 6.10). This implies that 56 (94.9%) of the 59 children had a discrepancy of pills using this pill count method.

This discrepancy in pills returned was expressed as a percentage of the total quantity of pills dispensed during this period, regardless of whether it is more pills or fewer pills than expected to give the percent discrepancy in ‘routine pill count’. The mean percent discrepancy for ‘routine pill count’ was 16.5 ± 20.4 , with a range of 0 - 87.5.

6.6.4.2 ‘Capped’ adherence

According to data collected on the 59 children who had complete information on ‘Pill count RRQ’, using the three cut-off points for adherence, just above a third appeared to be at least 100% adherent, above half were classified as $\geq 95\%$ adherent and slightly more than three quarters were classified as $\geq 80\%$ adherent (Table 6.10). Median adherence levels were 96.6% (Q1, 80.64%; Q3, 101.8%).

6.6.5 Comparison of adherence levels between the two pill count methods

Table 6.10 compares adherence levels between the two pill count methods. Some caregivers did not have information on the residual quantity of pills at last refill and hence their children,

though in the ‘routine pill count’ adherence group, were not included in the calculations of ‘Pill count RRQ’ adherence levels. This implies that those with ‘Pill count RRQ’ data were a subset of those with ‘routine pill count’.

Table 6.10 compares adherence levels between the two pill count methods. Adherence levels measured by ‘routine pill count’ were lower than those computed by ‘Pill Count RRQ’ at the 95% adherence threshold, taking 95% of doses. There were no significant differences in adherence levels at the 80% and the 100% adherence thresholds between the two pill count methods.

To make a comparison of the two pill count methods in the same children, a paired t-test was conducted on the 59 children who had data on both ‘routine pill count’ and ‘Pill Count RRQ’ and the respective percent discrepancy. Using the paired t-test, there was a significant difference between the mean adherence ($84.2\% \pm 27.9$) for ‘routine pill count’ and that for ‘Pill Count RRQ’ ($89.7\% \pm 24.3$), $t = -3.67$, $p = 0.001$. Similarly there was a significant difference between the percent discrepancy for ‘routine pill count’ ($18.8\% \pm 25.2$) and that for ‘Pill Count RRQ’ ($16.5\% \pm 20.2$), $t = 2.05$, $p = 0.045$.

6.6.6 Relationship between pill count adherence and reported adherence by the experimental ‘new 10-day tool’ and the control ‘PACTG-style tool’

Only child reports for ‘past 7 days’ adherence in the experimental group and child reports for ‘past 30 days’ in the control group were associated with pill count adherence. According to the Mann-Whitney U test, children in the experimental group who were 100% adherent for ‘past 7 days’ according to child reports had lower percent discrepancy for ‘routine pill count’ (mean rank; 11.7, $n = 19$) than those who were less than 100% adherent (mean rank 22.3 $n = 6$), $z = -2.34$, $p = 0.019$. This self-report adherence measure had fair ($\kappa = 0.339$) but non-significant ($p = 0.065$) agreement with dichotomised ‘routine pill count’ adherence at the 80% cut-off level.

Similarly children in the control group who were 100% adherent by ‘past 30 days’ child reports had lower percent discrepancy for ‘routine pill count’ (mean rank 28.5, $n = 55$) than those who were less than 100% adherent (mean rank 48.2, $n = 3$), $z = -1.97$, $p = 0.049$. This self-report adherence measure had fair ($\kappa = 0.218$) and significant ($p = 0.007$) agreement with dichotomised ‘routine pill count’ adherence levels at the 80% adherence cut-off level.

6.6.7 Relationship between pill count adherence levels and adherence levels measured by the MMAS-8

Using the student t-test, children with perfect adherence (score of 8) on the MMAS-8 had persistent but non-significantly higher pill count adherence levels than those with less than perfect adherence as shown in Table 6.11.

Table 6.11: Relationship between pill count adherence and MMAS-8 adherence

Pill count measure (%)	MMAS-8 score	n	Mean pill count adherence	t	P-value
‘Routine pill count’	8	89	89.7	0.607	0.545
	<8	37	86.3		
‘Pill count RRQ’	8	44	91.5	0.973	0.335
	<8	15	84.4		
Percent discrepancy- ‘routine pill count’	8	88	18.3	-0.335	0.738
	<8	37	19.8		
Percent discrepancy- ‘Pill count RRQ’	8	44	91.5	-0.337	0.737
	<8	15	84.4		

6.7 Factors associated with reported adherence

Factors associated with adherence were determined using ‘past 7 days’ child and caregiver-reported adherence in combined groups. Groups were combined to increase the power of the sample since there was no difference in adherence levels between the experimental and control groups. Table 6.12 shows the factors that were associated with adherence in univariate analysis at the 10% significance level.

Table 6.12: Factors associated with reported adherence for combined intervention and control groups

Characteristic	Categories	Taking less than 100% of doses by combined 'past 7 days' caregiver reports			Taking less than 100% of doses by combined child 'past 7 days' reports		
		Adherent n (%)	Chi-square	P-value	Adherent n (%)	Chi-square	P-value
Child changed household	yes no	86 (91.5) 142 (96.6)	2.933	0.087			
Primary caregiver education	primary secondary						
Relationship with primary caregiver	maternal paternal	63 (98.4) 48 (88.9)	4.785 ^a	0.046 ^b			
Child lost parent	yes no				76 (89.4) 11 (61.1)	9.07 ^a	0.007 ^b
Disclosure of HIV status to child	yes no	106 (98.1) 120 (91.6)	4.93	0.026	68 (89.5) 18 (69.2)	6.00 ^a	0.026 ^b
Use reminders apart from people to take pills	yes no	172 (96.6) 55 (88.7)	5.63	0.018	63 (90.0) 24 (72.7)	5.10	0.024
Knowledge of dose frequency	yes no	222 (95.7) 5 (62.5)	16.62 ^a	0.006 ^b			
Knowledge of time interval between doses	yes no	222 (95.7) 4 (57.1)	19.63 ^a	0.004 ^b			

^aPearson Chi-Square.

^bP-Value is for Fishers's Exact Test.

Having a maternal primary caregiver, having disclosed the HIV status to the child and using reminders other than people in taking medication, as well as knowledge of the dose frequency and time interval between doses, were all significantly associated with 'past 7 days' adherence by caregiver reports. Use of non-human reminders, disclosure of HIV status to the child and being an orphan were all associated with adherence by 'past 7 days' child reports.

In a logistic regression model of all factors associated with 'past 7 days' caregiver reported adherence, three factors were significantly associated with taking 100% of the doses: those who had knowledge of the frequency of dosing for all ARVs were 122.6 times more likely to be adherent than those who did not have this knowledge (Wald, 10.3; $p = 0.001$), those who

used another reminder other than people to take medication were 4.9 times more likely to be adherent than those who had no form of a non-human reminder (Wald, 5.58; $p = 0.018$) and those who had a maternal relative as primary caregiver were 2.8 times more likely to be adherent than those with a paternal relative as a primary caregiver (Wald, 5.4; $p = 0.020$). The only one factor significantly associated with child reports was loss of a parent, with those who had lost at least one parent (orphans) being 4.7 times more likely to be adherent than non-orphans (Wald, 5.8; $p = 0.016$).

6.8 Relationship between reported adherence and constructs of theoretical models

Mean scores on constructs of theoretical models that have been found to be correlated with adherence levels (Horne, Weinman 1999, Wolf et al. 2007, Gatti et al. 2009, Edwards 2006, Simoni et al. 2002, Gonzalez et al. 2004, Nicholson et al. 2006) are presented in Table 6.13

Whilst the majority of caregivers scored very high on beliefs about medicines, self-efficacy and moderating factors (potential barriers in the healthcare delivery or socio-economic environment), perceived social support scores were low with the median score falling below the half mark of the maximum possible scores (Appendix 5). More than three quarters had ART-related knowledge that was above average (above 50% of scores), and included knowledge of names of drugs, doses, dosage intervals, and the implications of non-adherence on CD4.

Table 6.13: Median scores on constructs of theoretical models

Construct	Median score (inter-quartile range)			Range of possible scores	P-value ^b
	Experimental ^a	Control ^a	Total ^a		
Beliefs about medicines	53 (48-57)	54 (50-57)	53 (48-57)	12-60	0.617
Self-efficacy	72 (70-72)	72 (70-72)	72 (70-72)	0-72	0.709
Social support	14 (10-18)	13 (9-17)	13 (9-18)	0-28	0.300
‘External’ factors ^c	41 (39-42)	41 (38-42)	41 (38-42)	9-45	0.999
ART related knowledge	7 (5-8)	7 (5-8)	7 (5-8)	-1 to 10	0.777

^aParticipants with non-responses to one or more items on each construct are not included

^bMann-Whitney U test

^cModerating factors specified in the Information Motivation Behavioral Skills model (Munro et al, 2005)

Caregiver ART-related knowledge was assessed including names of medicines the child was taking (proprietary or non-proprietary), dose and dose interval, and knowledge of treatment-related aspects such as the meaning of the CD4 count, viral load and resistance (Wolf et al. 2007) (Table 6.13)

Adherence levels measured using ‘past 7 days’ and ‘past 10 days’ adherence in the experimental ‘new 10-day tool’ group and those measured using ‘past 7 days’ and ‘past 30 days’ in the control ‘PACTG-style tool’ group for both child and caregivers were assessed for their association with caregiver reported social support, environmental, beliefs about medicine, self-efficacy and knowledge scores. Only ‘past 7 days’ child reports by the experimental ‘new 10-day tool’ were associated with caregiver social support scores. Children who were 100% adherent using ‘past 7 days’ child reports in the experimental 10-day tool group had higher scores (mean rank = 26.7, n = 44) than those less than 100% adherent (mean rank = 14.6, n = 8) using the Mann-Whitney U test ($z = -2.4$; $p = 0.016$).

6.9 Findings from focus group discussions

6.9.1 Importance of ART

ART was perceived as a life-transforming and life-saving medication. This was emphasised across all groups of children as well as caregivers. Caregivers highlighted the transformation they had seen in their children from being very ill, deemed to die and helpless, to a child whom they can send to do some household chores. They perceived that the improvement in health, as a result of treatment, was also linked to adherence to the medication regimen.

“Her health is now good, she is now like other people. If I don’t talk about her condition, no one will know, so I think it is good to take pills.” (Caregiver)

“I saw that pills were important in that when I started taking them ah ah ah (laughs). I never thought I would be able to live, but when I started taking the pills following the timetable, I started to do heavy work.” (Child)

“Pills are important in that during the first time that I started to take them I was not able to do anything but when I started taking the pills I started to recover. I was now doing other activities/jobs that I was not able to do.” (Child)

The importance of ART and its effect on improving quality of life were realised and valued more because children seemed to start ARVs at late stages of the disease.

“I was very sick when I started coming to the clinic and I got admitted. When I was discharged I went home and I spent 3 weeks unable to do anything. When I was introduced to the pills I went home and started to do work.” (Child in a very faint voice)

Improvement in weight was one of the most appreciated outcomes of ART and was considered a great marker of improved health. Some children had to receive nutritional support to boost their weight.

“What makes me happy on the issue of pills is that, my grandchild used to spend most of her time sleeping. She was very weak, so she was not able. When she started taking ARVs I see that she is feeling much better and her weight is improving.” (Caregiver)

6.9.2 Types of non-adherence

The discussions revealed the existence of both intentional and unintentional non-adherence in the participants. Intentional non-adherence was mainly as a result of children not being willing to take ARVs. Caregivers explained that children may refuse to take ARVs when the caregiver offers them the medication, or may pretend that they have taken their medication when in fact they have thrown the dose away. Caregivers may fail to support the child in taking medication due to lack of appreciation of the value of the medication or due to lack of care for the child.

“When I gave him he refused so I told him that if he does not take them it will be his own problem, there is another day that he went to school without taking his pills and he came back very sick. Then I told him that it was his own fault, right now he takes the pills before going to school.” (Caregiver)

Unintentional non-adherence was reported to be mainly a result of forgetfulness or as a result of child or caregiver being busy, having travelled or being away from home doing daily activities. Routine activities such as child and caregiver going to work in the crop fields or child playing at another home were widely mentioned as causes for unintentional non-adherence

“We would have left very early before the sun even rises. Sometimes you would have gone to areas like Chavatama to get clay soil for making clay pots and you would have left the pills at home, then you come back when the sun is like-like, meaning the sun will be high above, then this will not work.” (Child)

Interval non-adherence may be as a result of children having no watches or clocks to keep track of time. Children reported using the sun or other time indicators such as time for cattle to get into the kraals, with the times varying widely with the seasons of the year.

“It is not easy for me because I do not have a watch. I may take my medication when the sun is high. I might forget when I go to the fields and forget to take the pills, but during the evening I take my medication when I eat, when we take our meals. We might come around 10:00.” (Child)

6.9.3 Barriers and facilitators of adherence

Children and caregivers were able to make a link between adherence and improved outcomes as well as the consequences of non-adherence. They stressed the importance of both taking all the doses and taking them at the required intervals.

Several factors were identified as enhancers of or barriers to, adherence to ART in children. These were reported by both caregivers and children, and were based on their experiences with taking ARVs.

6.9.3.1 Responsibility for medication adherence

Success in adherence to medication was shown to be the result of combined responsibility between child and caregiver. As the child grows older, s/he assumes more responsibility. The first responsibility is to remind the caregiver to give him/her medication if not yet old enough

to take medication on his/her own. The child may bring the medication to the caregiver for supervised administration or for administration by caregiver.

“I have a child who is six years, she comes to me and ask for her pills. When she finishes eating before she goes to school she will ask for her pills. In the evening if she finishes eating she checks the time and if I also checked mine, most of the time she is the one who comes to me to ask for her pill, because I just ensured that she take the pill on her own.” (Caregiver)

When the child is old enough to take medication, the child assumes more responsibility. The supervisor acts only as a reminder to medication-taking. At times the caregiver may need to directly observe the child taking the tablets.

“My child is 11 years old, sometimes she takes the pills on her own sometimes she forgets, but most of the time you remind her when it is time for taking pills. But she will take the medication on her own. She is now able to take medication on her own. She just needs to be reminded when the time is up. Because she is now 11 years, sometimes she might have gone out and she will take them some time later.” (Caregiver)

“My mother will ask you if you have taken your pills, if you say no she will tell you to take them while she is watching you.” (Child)

There were instances when a caregiver reminded the child to take medication and the child pretended to do so and threw away the tablets. This aspect was only raised by caregiver groups and not by child groups. However it also emerged from both child and caregivers that the child may miss doses whilst the caregiver is not aware of this, and it can only be noted at the clinic either during pill count or self-reports.

A good child-caregiver relationship enhances adherence since there is good communication and the child is free to remind the caregiver about medication-taking.

“The child must be friendly and should find it easy to relate to you so they can be free to remind you.” (Caregiver)

6.9.3.2 Disclosure of HIV status to children

It was noted that disclosure of HIV status to children, as well as an explanation of the importance of taking medication everyday on time, can enhance the child's co-operation on medication-taking. A child who understands why s/he has to take medication acts as a reminder at dosage times and can act in a way that facilitates adherence.

"My child found it difficult at first. I did not tell her that she was supposed to take the pills in order for her wounds to be healed. I did not tell her but now she reminds me when she has not taken her pills, then I will tell her if the time is not yet up to go and play. During the first days she did not like the pills but with time when I explained she started liking them, sometimes she takes the pills on her own, then I would help by monitoring her as she takes the pills." (Caregiver)

There was, however, a lack of consensus on the age for disclosure, and what to disclose at certain developmental stages of the child. Whilst some caregivers felt that six years could be the right age for disclosure of HIV status to the child, others argued that at this age, a child may be told that s/he needs to take medication for survival but may not understand what it means to be HIV positive. These argued that the age for disclosure of HIV status can start at 12 years, whilst others said it can start at ages as late as 14-15 years. Children 13 to 15 years, however, pointed out that when their HIV status was disclosed to them, this helped them to understand their condition and accept the fact that they will need to take medication for a long time.

"I check maturity according to each child, for example how much the child understands. Another child might understand at an age like 7. For example I have a child at home who is 7 but is very understanding. She is not taking pills but she understands it."

"But she does not know what it means."

"Yes she does not know what it means at that age. At 14 she will know"

"I am thinking 12 and above."

“I think at 6 she will be able to understand what the pills that I give her are for what. Because sometimes I would not be at home so she will take on her own.”

No she does not refuse to take her pills but she does not know what it means.”

“... My child is 3, I will tell her at 6.” (Caregiver conversation)

“If I tell him at his age he cannot understand but from 15 years it is easy.” (Caregiver)

Caregivers find themselves not skilled enough to disclose HIV status to the child. They are not sure how best to communicate the message in a way that the child will understand his/her condition and they also have fears of the child unnecessarily disclosing to other people the fact that s/he is taking ARVs.

“Some people disclosed to the child who was 12 years old and he drank rat poison and he died. You can tell them gradually and show them other children who are also ill.” (Caregiver)

“In my opinion it is difficult for a child to know of her status at this age. It is difficult for me I do not know how to tell her. Maybe the child might go around telling people saying, “Haa I am taking pills, I am taking pills”. She will say a lot of things. So I think that I will wait for the child till she is mature.” (Caregiver)

“I did not have any challenges from the beginning. When her mother was giving her pills before she passed away, she said they were sweets. So now she would say “grandmother I want my sweets”. The mother used to take the tablets saying that they were for TB while they were ARVs. Right now she even takes the pills even when I am not around, she knows the time.” (Caregiver)

6.9.3.3 Stigma and discrimination

More stigma than discrimination was disclosed during the discussions with both caregivers and children, and this emerged across all five groups regardless of whether rural or urban. Stigma was detected in both open statements of ‘labelling’ from community (including community leaders) and from other school children. The most common labelling mentioned Triviro®, a fixed dose combination (FDC) containing the most common regimen that was

being prescribed to these children which includes NVP, stavudine and lamivudine. Children and/or their parents/caregivers are sometimes referred to as ‘pill-taking’ people. However it emerged that whilst some get affected by this and avoid disclosing the child’s condition as well as making an effort to hide medication-taking, others would not be so mindful of this stigmatisation from the community, neighbours or fellow scholars. The direct impact of stigma on adherence was not well established during the discussions but there is a potential impact mediated by fear of disclosure of both HIV status and, more likely, the fear of being seen taking ARVs.

“While you are walking people of your age will be laughing at you, they will call you "mai maTriviro (Meaning mother to Triviro)." They will ask, "did she take her pills?do not listen to her she acts like she is not normal" (shyly she laughs) " She did not take her pills before she came here" They would start to look down upon you.” (Child)

“Haah as for me there are a lot of people who laughed at me. When we are playing, if you do anything that is not free, they will just say it is because she is taking Triviro (pills.) (Child)
Some will humiliate and scorn at you, they will give you a nickname, Mai MaTriviro, (meaning the mother to Triviro®).....” “Young ones” (two in unison) “and adults as well.”

Community leaders were also noted to stigmatise people living with HIV/AIDS. A woman from the rural study site of Murambinda quoted one of the village heads saying the following statement during distribution of food that had been donated to communities that are prone to hunger.

“You people with AIDS we will not give you food. Isn’t it that you are being given some food already?” (Caregiver, quoting the village head)

“They may use the status against you. If you come to the hospital they may say, ‘she went with a child who has AIDS.’” (Caregiver)

Whilst stigma was reported to be from community and school children, it emerged that even the caregivers may stigmatise the child they are caring for.

“You can hear a caregiver saying ‘You, you are a pill-taking child and so quickly come here and take your medication, do not bother me’. The child may be hurt and lose interest.”
(Caregiver)

“Sometimes when you are living with your relatives they won't accept it. They will ask you why you are always taking pills, so when they know (that you have HIV) they will laugh at you.” (Caregiver)

“I know that it is difficult when there are people that you live with. Let's say you are renting a house and at that house there are people who do not know about it. When they begin to know, they will say bad words about your condition. Let's say they do not have a relative who is taking pills they will say words that are painful to you.” (Caregiver)

6.9.3.4 Type of medication

Caregivers found it much easier to use the pills (solid dosage forms) than the liquid medication. However, at the time of the study, almost all children were on solid dosage forms of ARVs.

“I think that pills are easier to use than using liquid medication because when the bottles are many you will end up taking from each of every bottle but with pills if it is 1½ it will remain 1½ and it is easy to carry a single packet of pills.”

6.9.3.5 Economic factors

Economic challenges emerged as one of the causes of non-adherence, but these were mainly to do with failure to take medication when there was no food available to eat. There was unwillingness to take or give medication prior to the child eating. Whilst transport money to go for review visits often proved a challenge, caregivers showed dedication to their children and determination to have their children survive by travelling long distances to the hospital and back.

“Food is another problem. When there is no food people do not like tablets because they irritate them without food. So they can cheat and place them under the pillow, because they also give instructions on other tablets which are not ARVs so we think it is the same with ARVs.” (Caregiver)

“It is difficult for me because there will be no food at the time that I would want to take my pills...energy giving foods, if you take the pills without eating you will get weak.” (Child).

“.....She (the child) was diagnosed of TB and kwashiorkor. She started receiving TB tablets while in hospital. She was also HIV positive. She spent a week admitted and then was discharged. I was travelling everyday on foot from Highfield, in the morning to feed her. In the evening I would come again on foot to feed her. I was also sick but I had to be strong for my grandchild to be well..... I have been taking pills from 2006 till April 2009 this year. I went to the doctors and they referred me to Nazareth so that I could start my course again, because I had defaulted ta my medication. The reason I stopped taking my pills was that I didn't have money to pay for the card because going to get the pills was easy because I could walk to Old Highfield, but I failed to get \$1 to pay for the card.” (Caregiver)

6.9.3.6 Social support

Social support emerged as one of the key enhancing factors to adherence and was intensely mentioned across all groups of adults and children. Other family members, neighbours and siblings provide support through reminding the child to take medication and take the caregivers role when s/he is not at home. Siblings, even younger ones, can take the role of reminding and ensuring that the child takes his/her medication when it is due.

“I stay with my younger sister...but ah... It is easy because if I do not tell her that I am taking my tablet she will just leave me.... If I get sick, and she knows it, she will just say sister we have to go to the clinic because there might be a problem that needs to be solved at the clinic.” (Child)

“I found it easy because I taught other family members (my other children) to give my grandchild medicine but I had to limit travelling but they may not do it correctly.” (Caregiver)

Having other children and adults who are also taking medication in the household provides support since it becomes a group activity to take tablets. This is particularly so if the dosage frequencies are the same.

“I do not see any difference because when it comes to time for example when 7 o'clock is the time for taking pills. When that time is up you see all the children who are in the programme will take their pills.” (Caregiver)

“I haven't met any challenges because I just take my pills even when people are there. Even when I go to the rural areas where my husband's relatives are present, I also disclosed to my father in law, when my husband got sick, I told him about the sickness because there is also my big brother in law.” (Caregiver)

Adherence was said to be a lot easier for the child if the caregiver was also taking medication

“As for me, in terms of missing taking pills.....I believe that if the mother has been tested and knows her status she will not skip or stop giving her child pills because she is supposed to take her pills and it also means that the child also takes the pills the same time with her.” (Caregiver)

“I see it is very easy because as for me I am a mother, I am also taking pills so I would not forget, and we have the same time table so it is the same.” (Caregiver)

Stigma and non-disclosure of child status, especially to neighbours, was identified as a barrier to creating adherence social support networks with neighbours, with other extended family members and also from those who are sharing the same house through renting of single rooms in a multiple roomed house, a phenomenon that is very common in the high density suburbs in urban Zimbabwe.

Maternal orphans receive much of their care and support from the maternal relatives, with the paternal relatives being less caring.

“If you go to their home in Seke they won't be there. If I call them they won't respond but in our family, her mother's family, there is no problem. The father does not know that their child is sick, since the death of the mother, they asked her younger sister (of the late mother) to take the child and she came back with wounds without any treatment received, and I told him, but he did not do anything, I thought that if he would come, I would tell him the situation. If you call him he does not pick up his phone.” (Caregiver, maternal aunt)

And the other thing is that I told the father of the child of the child's condition but he did not accept it, he is saying "I don't know where the mother of the child got it" (HIV). But I stay with all the four children with me. I struggle to get food; I just get a little amount of food so that the child might just have something to eat. The father has got another wife. I don't get much assistance from the father of the child because he doesn't care. Now because I walk on foot from Highfield, yesterday I was in bed because of a back ache. I try very hard to take care of the children because there is no one except myself." (Caregiver, maternal grandmother)

"I think taking pills is good. For example, this child that I have is my sister's child. My sister got sick and she died. I did not know of her sickness. I tried to get to know the cause of the sickness till she died. When she died her child was sick so I was staying with her, I became relaxed so I realised that I was neglecting the child by not visiting the clinic." (Caregiver, maternal aunt)

6.9.3.7 Period since initiating ART

Caregivers and children highlighted that adherence is difficult soon after initiating ART but improves with time. When the child is put on ART for the first time, there are lot of issues to be resolved; including making sure that the child understands why s/he has to take medication all the time and understanding as well as managing side effects.

"It is usually difficult when you are getting your pills for the first time because you won't be used to them so you might forget the time to take the pills. If the child reacts to the pills you might think that the pills are not working. The child might develop rash or wounds when receiving the starter pack for her/his medication and then you would wonder what would have caused that to happen, this can be difficult for you and then it will become easier later on with time." (Caregiver)

6.9.4 Disclosure of non-adherence to health workers

Adherence monitoring at health facilities is assessed through self-reports and pill counts. There was awareness that if there is discordance between adherence through returned pills and self-reports, the health workers might query this discrepancy. It was evident that both children and caregivers would get very uncomfortable when this happens, a clear indication that they do not want to appear that they are behaving in a socially undesirable manner.

“Nurse I would want to answer that one. It happens because I have experienced it. I asked her (the child) whether she was taking her pills and she replied, 'Yes'. So when I came to the clinic, the nurse told me that the child was not taking her pills. She showed the nurse the pills, I thought I was clever and did not know that the pills can actually show you that someone is not taking them. So I think it's better to tell the truth.” (Caregiver)

“They ask (laughs) but I bring the empty containers.”

“It happens for example they might have forgotten to take their pills, then when they are asked they say yes I took all, they will ask for the container but they will say they left it at home (child). They will be afraid of being asked to start taking the tablets again.”

“Nurses will ask (whether I missed doses) but it has never happened that I lied because you bring the empties.” (Child conversation)

“It is two way, you should be polite and they should also take your point. It happens that you may not say the truth. But if you tell lies it does not help.” (Caregiver)

There were three reasons identified for incorrect reporting of non-adherence behaviour. Whilst there was an appreciation that disclosure of non-adherence is necessary for the child to receive better care and treatment from the health facility, caregivers may still fail to report that the child missed some medication doses. One of the reasons is simply forgetting that the child had missed doses, especially when the doses were missed several days before visiting the clinic.

“I think it is possible that you can forget that the child once missed his/her pills because the day that you would have skipped is not the same day that you have gone to collect the pills. Waiting for a date like 10th, you might forget that the child once skipped his/her pills on a certain date.” (Caregiver)

There is fear of disclosing non-adherence to health facilities. Fear of victimisation hinders some caregivers and children to disclose non-adherence, despite appreciating that it is not good to avoid telling the truth about non-adherence.

“It is not easy (to disclose non-adherence) because they can shout at you... the nurses, yes she shouted at me.” (Child)

“Sometimes you explain, then they say you did it on purpose, “some people need these medicines but you are being negligent.”, so it depends on how you tell them. Some health workers are not polite so it is difficult to tell them.” (Caregiver)

“As for me I see that yes it is difficult for me, but what I then do is that I first look at the person that I am talking to, to see if he or she is not going to shout at me, but I know that it is good to come out in the open to tell the truth that the child missed or skipped his or her medication. For example this child that I have here, after you bath/wash her, you may realise later that the child has gone to school without taking the pills, she did not take her pills after she had left for school.” (Caregiver)

Interestingly, it also emerged that whilst both caregivers and children find it difficult to disclose non-adherence to health facilities, there are also children who feel reluctant to tell their caregivers that they did not take their tablets. This is an indication that children at times assume full responsibility for taking medication and when they do not, the caregiver might not know of this non-adherence. Caregivers also explained that children may pretend that they have taken their medication when in fact they have thrown the dose away.

“I do not talk about it because they will ask my mom, why I have skipped my medication, still she will just say I told her to take her medication.” (Child)

“You just keep quiet; you do not talk about it, you do not tell anyone, even your mom.”

It was clear that it can be difficult to report a behaviour that is not socially desirable and acceptable to health workers. Reporting non-adherence for a child is perceived as portraying an image that is not expected of a caring mother.

“I know it is not easy to say it but you have to say it, but it will be difficult for you to say it, because they will say that how can a mother forget to give pills to her child, but you have to say it for other procedures to be taken for the period that the pills have not been taken.”

Others, however, would disclose regardless of this fear, desiring that their children receive better care which is based on correct information.

“To tell the honest truth, on the 28th of this month they asked me if the child had ever skipped/stopped taking the pills then I said "yes", I had gone to a funeral, and they asked me if I had spent the whole day at the funeral and then I said yes. I said the honest truth because it is good to be honest.” (Caregiver)

“As for me I would like my child to recover, but if I don't want my child to recover I would not tell the truth. So I will come to a point when I will say, "ahh don't scold me because I forgot to take my pills yesterday, it can just happen". Even if they shout at me, I would have said the truth.” (Caregiver)

6.9.5 Perceived quality of care at health facilities

There was an expression of appreciation of the services provided at health facilities. The health facilities are identified as life serving centres with dedicated staff, regardless of their poor remuneration. Even when health staff expressed anger for poor behaviour, this is perceived as an expression of concern for the child's health.

“I think that the help we get here at the hospital is friendly to children because, I haven't failed to get the pills” (Caregiver).

“When she (the child) got here she was admitted and she was in ward E2. She started to receive treatment. The doctors have a great job. God should give them the strength to keep on doing the job. God should give them love, because the child was no longer eating and she was vomiting. The doctor had courage to put a tube through her nose. They wrap up the tube, but she was removing it and they were to cover her hands. They remained strong.” (Caregiver)

“I just think the government should give doctors and nurses better salaries because they do a great job. The only job that I know that is difficult is the one that they do.” (Caregiver)

6.9.6 Timing of initiation of treatment

It emerged that children were initiating treatment at advanced stages of the HIV disease. The main reason for this appeared to be late presentation at ART-initiating sites. Some children were only identified to be in need of ART when they were so ill that they needed admission or when they were already very ill and had very little strength to do their normal chores.

“I am also thankful and I like it. I have my grandchild here, I am saying that pills are good for sure. My status is built by this child. This child's mother passed away. She was sick and she died. The mother left her child sick. I think I just spend one week after the burial of the mother, people were thinking that they would come again to the funeral of the child.”
(Caregiver)

6.9.7 Medication-handling behaviours

There were some challenges with medication-handling which affected adherence assessment. Some children were noted to have a habit of pretending to take medications but then throwing them away. Medication may be removed from usual containers and put into smaller containers during travel. Storage challenges were noted in that the child may fail to locate their medicine. There is a practice of putting medication in separate containers and keeping it in separate places for fear of losing all the medication through theft.

“When travelling you take pills according to the number of days of your visit. If you are going to spend two days then you take the pills that are enough for two days.” (Caregiver)

“I put them in different places so that if other pills are stolen I am left with some, let's say the other pills are in the hand bag, then I will have to place others somewhere else.” (Caregiver)

“I have my sister's child... when given tablets and asked to get water outside, he throws away the tablets and drinks the water.” (Caregiver)

“I asked if he had taken tablets and he said no. I asked him to take but he pretended like he was taking, folding in his hand as if he had them in hand but I realised there was nothing in his hand. He wanted to take only part of the dose and leave the other and now it is okay.”
(Caregiver)

CHAPTER 7: DISCUSSION

7.1 Introduction

Adherence to ART among children remains a critical component in the fight against HIV and AIDS. Although there are now more effective interventions to reduce MTCT of HIV (Ciaranello et al. 2013, Chigwedere et al. 2008), children continue to be infected despite interventions or because of lack of access to preventive services by the mother for various reasons. In Zimbabwe, an estimated 9300 children were newly infected with HIV in 2012 (UNAIDS 2013b). This study reveals that adherence monitoring continues to be a challenge in our study settings with those methods that are affordable in LMIC presenting substantive feasibility, validity and reliability challenges.

7.2 Adherence levels among children on ART

Reported adherence in my study was very high and falls within the wide range of child- and caregiver-reported adherence levels that have been found in literature in both the HIC and the LMIC. Reports of full (100%) adherence by caregivers in my study range from 89% - 98%, across varying adherence periods. In the past decade, studies published on research conducted in HIC showed that 75% - 100% of caregivers reported full adherence over varying adherence periods (Albano et al. 2007, Farley et al. 2003a, LePrevost et al. 2006, Martin et al. 2009). Similar proportions of caregivers (72% - 99%) from studies published in sub-Saharan Africa in the past four years reported full adherence (Bagenda et al. 2011, Biressaw et al. 2013, Iroha et al. 2010, Mghamba et al. 2013, Weigel et al. 2009). Again, similar to my study, high adherence levels were reported for children 1 - 14 years in rural and urban Kenya, 98% perfect adherence over the 'past 7 days' by caregiver reports (Vreeman et al. 2009). However in another study in Western Kenya, about 73% of children between 0-14 years had reports of perfect adherence with adherence being measured over different times (Vreeman et al. 2008a). A recent research publication on adherence to ART among children aged 2 - 16 years conducted on three continents showed that full adherence for 'past 3 days' caregiver reports were reported in 96% of children, findings that resemble those in my study (Harrison et al. 2013).

Although several studies have been conducted on antiretroviral therapy in children in Zimbabwe, not many of these have assessed adherence to ART in this age group (Walker et al. 2012). A few more studies that have been conducted on adherence to ART in children in Zimbabwe (Campbell et al. 2012, Ferrand et al. 2010, Mavhu et al. 2013, Muyingo et al. 2008, Skovdal et al. 2011) focus mainly on qualitative aspects of adherence. Nevertheless, some of these studies (Albano et al. 2007, Campbell et al. 2012, Ferrand et al. 2010, Mavhu et al. 2013, Skovdal et al. 2011) were conducted at a similar time period to my study, and hence comparisons can be made within the historical context of the offering of ART services in Zimbabwe.

At the 95% adherence cut-off points, my study showed adherence levels of 96% by caregiver reports for ‘past 10 days’, ‘past 14 days’ and ‘past 30 days’, a proportion close to that observed in a recent Ethiopian study (Biressaw et al. 2013) and that falls within this range of 66%-100% as per studies from LMIC. A year after conducting my study, Chimhuya, Nathoo and Rusakaniko (2012) conducted a study at one of my study sites and reported that 93% of children below 10 years of age were adherent to ART at 95% cut-off point by ‘past 30 days’ caregiver reports, again supporting the findings reported in my study (96%).

Müller et al (2011) in South Africa found that 92% and 90% of caregivers reported the children taking more than 95% of doses using the ‘past 3 days’ recall period, and using VAS respectively. In my study, those who were 95% adherent were considered ‘adherent’ in contrast to Müller et al. (2011) who included these in the non-adherent group, a factor that may further complicate comparisons of adherence levels. This shows that classification of adherence based on specified adherence cut-off points such as 95% differs slightly amongst researchers, who may either include those who are 95% adherent as ‘adherent’ or may view these individuals as ‘non-adherent’, introducing possible slight variations in adherent proportions. Other studies in the Southern African region showed that 86% (Davies et al. 2008) and 84% (Haberer et al. 2011) of caregivers gave reports of children being adherent at the 95% cut-off point, proportions that are lower than those in my study. In two studies conducted in India, however, caregivers reported widely varying adherence levels at the 95% cut-off point of 66% and 99% (Bhattacharya, Dubey 2011, Seth et al. 2013). In Uganda, the proportion of adherent children at the 95% cut-off point was quite high (99% - 100%) (Bagenda et al. 2011).

Child-reported adherence levels in my study were high, with 88% and 94% of children reporting adherence levels that were $\geq 95\%$ for the maximum adherence assessment period, in the experimental and control groups, respectively. My study, however, showed that child-reported adherence was lower than that reported by caregivers, a finding consistent with other similar studies such as that of Harrison et al (2013) who reported that more children reported non-adherence than adults. Although Martin et al (2009) also reported lower adherence levels by child reports than by caregiver reports, the difference between the two was not statistically significant. Since few studies have assessed adherence by child reports (Kahana et al. 2013, Martin et al. 2009, Vreeman et al. 2008b), comparisons of adherence levels by child reports in my study with those in other studies was limited.

Apart from using multiple adherence recall periods, my study used several adherence cut-off points and this generated adequate information for logical comparison of adherence with those from other studies that have used varying adherence cut-off points. Dichotomized adherence cut-off points of 80%, 95% and 100% were used as appropriate for the specific analyses and for comparison with other studies that only reported specific cut-off points. Child- and caregiver-reported adherence levels have been shown to vary widely and can be influenced by the adherence cut-off point, the type of the instrument used to collect adherence data (Garber et al. 2004), the adherence recall period (Lu et al. 2008) and the age of the child. Mavhu et al (2013) noted that adherence levels decreased from 76% in children below 13 years to 55% in children above 16 years. However, this association between adherence and age was not significant after controlling for other factors, signifying that the nature of analysis of data conducted in a study has significant influence on the levels of adherence measured, hence caution should be exercised when comparing research findings from different studies. Special selection criteria may also cause variations in adherence. As an example, Davies et al (2008) only included children whose caregiver had kept the last three clinic appointments, a factor that may have introduced bias resulting in slightly higher adherence levels than those found in the general population in this study setting.

In my study, pill count adherence levels at the 95% cut-off point were far lower than those in other studies, with only 39% and 58% of those children with adequate information on pill count data having attained $\geq 95\%$ adherence using the 'routine pill count' method and the 'Pill count RRQ' method, respectively. Studies in Southern Africa have variously reported 69% (Haberer et al. 2011), 75% (Davies et al. 2008) and 90% (Müller et al. 2011) of children as

being adherent at the 95% cut-off level. Studies in sub-Saharan countries and in other HIC that utilised only clinic-based pill count/medicine return adherence levels at this cut-off point showed even higher (88%-97%) adherence levels among children on ART than those found in my study (Hien et al. 2013, Mghamba et al. 2013, Seth et al. 2013). Dichotomised adherence levels at the 95% cut-off point in my study were only found to fall within the range of unannounced home-based pill counts/medicine measure adherence reported in past studies, which show $\geq 95\%$ adherence levels in less than 40% of children on ART (Biressaw et al. 2013, Haberer et al. 2011) although the home-based pill counts have been noted to also yield higher adherence levels in another study (Bagenda et al. 2011).

Contrary to dichotomised adherence levels, which were lower in my study than other past studies using clinic-based pill counts/medicine measure, median adherence levels for 'routine pill count' (91.4%) and 'Pill count RRQ' (96.6%) were similar to those obtained in past studies in children (Hien et al. 2013, Martin et al. 2009). This central measure of adherence may be of limited use in quantifying the specific number of children that fall below a specified critical adherence level. The median adherence level was also found to be very high (93%) for unannounced home-based pill counts when the dichotomised adherence level at the optimal 95% adherence level was low 38% (Haberer et al. 2011). In a South African study, median adherence measured using returned syrup was above 100% showing that this measure is of limited use in quantifying the proportion of those children who critically need adherence interventions.

Complexities in comparisons of adherence levels from different studies may arise from this use of dichotomous versus continuous adherence measures. When reviewing and comparing adherence levels, each of these types of adherence levels must be compared separately. Similar to the differences noted in comparing dichotomised or median pill count adherence levels within our study, Haberer et al (2012) again reported median adherence levels of 100% by 'past 3 days' caregiver reports, 97% by 'past 30 days' using a VAS, 97% by unannounced pill counts and 96% by MEMS[®] and yet only 89%, 68%, 61% and 56% of the children, respectively, had $\geq 95\%$ adherence. This is clear evidence that only like measures of adherence should be used to compare adherence levels.

Facility-based pill counts in my study revealed far lower adherence estimates than self-reports, a finding supported by a review (Vreeman et al. 2008b). In contrast, facility-based

pill counts have sometimes been found to overestimate adherence, yielding adherence levels that are similar to self-reports (Minzi, Naazneen 2008). In a study conducted in the USA where adherence assessed by several measures, including pill counts, was very high, adherence levels by facility-based pill counts were similar to those measured by MEMS® (Martin et al. 2009), a measure that is consired as a gold standard but was not affordable for my study that was conducted in a low income country.

7.3 CD4 measurements and self-reports

In my study, CD4 cell counts collected within 7 months of adherence assessment were found to have no association with adherence behaviour measured by both child and by caregiver reports, an observation similar to that found in a past study (Van Dyke et al. 2002). This analysis was not considered to be predictive validity since the CD4 measurements were conducted prior to recruitment into the study and before the adherence assessment period and this measurement was based on the assumption that children who have a higher CD4 count are generally adherent and will sustain this bevavior over time, or conversely, children who have a lower CD4 count would then receive counselling and would be more adherent in the future. This hypothesis was rejected, however some past studies that have explored the predictive relationship of CD4 measurements to adherence produced similar results. Martin et al (2009) found that CD4 count and CD4% were not associated with either caregiver or child reports and Mathews et al (2002) also noted the lack of association with the use of an AACTG tool in an adult population.

The nature of the association between CD4 counts and adherence, nevertheless, has generated conflicting results, although the majority of studies showed no association between self-reports and CD4 measurements. Liu et al. (2006) found that CD4 count can predict adherence behaviour in adults when adherence is measured using self-reports, contrary to the findings in the child population in my study. Moreover, CD4 counts have been found to be correlated with adherence measured by objective measures such as MEMS® when pill counts and child and caregiver reports did not (Martin et al. 2009), providing conflicting information on CD4 measurements as a proxy for adherence, or casting doudbt on the accuracy of pill counts and reported adherence as predictors of immunological outcomes in HIV disease.

Although my study did not explore the relationship between self-reports and other biological measures such as virological outcomes, similar conflicting findings have been noted in studies that have explored the relationship between self-reports and virological outcomes (Farley et al. 2008, LePrevost et al. 2006) in children on ART.

7.4 The validity and reliability of the ‘new 10-day tool’

Owing to the extremely high cost of MEMS[®] and the prevailing difficult macroeconomic conditions that rendered the use of MEMS[®] unaffordable for my study, I explored the use of a superiority RCT to establish if the new tool would be superior in detecting non-adherence. The ‘new 10-day tool’ was a tool that was designed in my study following literature-based recommendations for improving the accuracy of self-report measures (Gagné, Godin 2005). The recommendations were based on the acknowledgement that self-report measures of adherence have been found to be subject to social desirability and recall biases. Self-report adherence measures have been noted to have high sensitivity and low specificity in evaluating adherence behaviour, identifying almost all those who are adherent as such but having a lower capacity to detect non-adherence behaviour (Müller et al. 2011). This characteristic may be ascribed to social desirability bias, with patients who are adherent readily reporting this desirable behaviour, whilst some of those who are non-adherent may also report full adherence, thus avoiding the need to report undesirable behaviour.

Although pill counts have been used to validate self-report measures in several studies as cited by Svarstad et al (1999), in my study pill counts were not used for validating the new self-report tool since I was also assessing the pill count method for its feasibility and accuracy.

In line with other studies that have conducted self-reported tool validation (Mannheimer et al. 2008, Davies et al. 2008), an adherence cut-off point of 100% was used for all self-report measures in validity and reliability testing of the ‘new 10-day tool’ since self-reports have high sensitivity and low specificity. A study conducted among children on ART in South Africa reported constant high sensitivity across several adherence cut-off points whilst specificity was low, increasing with higher adherence cut-off points (Müller et al. 2011). However, in my study all adherence cut-off points and assessment periods were used in comparing adherence levels between the experimental ‘new 10-day tool’ and its comparator.

7.4.1 The ‘new 10-day tool’ compared to the current ‘PACTG-style tool’

The ‘new 10-day tool’ did not show any superiority against the ‘PACTG-style tool’. My study did not show a statistically significant difference in adherence levels measured by the ‘new 10-day tool’ with those measured by its comparator, the ‘PACTG-style tool’. Based on the mathematically derived assumption that significant differences in reported adherence levels measured by two different tools in the same population are most likely to reflect changes in specificity of the tool, my study did not demonstrate that the ‘new 10-day tool’ had improved capacity to identify non-adherent children over and above those identified by its comparator, the ‘PACTG-style tool’, using both child and caregiver reports. It could not, therefore, be demonstrated that this tool was superior to the ‘PACTG-style tool’ using a RCT design.

Failure to demonstrate a significant difference in adherence levels between two self-report tools was also reported in a previous RCT that compared an AACTG-style tool to a past 7-days general recall adherence instrument (Mannheimer et al. 2008). There are, therefore, challenges to address in designing a self-report tool that can overcome the barriers to reporting non-adherent behaviour more accurately than currently widely-used ACTG-style tools. This may be achieved by reducing the social desirability and recall biases (Gagné, Godin 2005), two types of bias that have been identified as the major cause of overestimated adherence levels when assessing adherence using self-reports.

Although my study could not demonstrate that the new ‘new 10-day tool’ was superior to the currently used self reports, adherence levels in this new 10-day tool were not significantly lower than those of the comparator, the ‘PACTG-style tool’, showing that the ‘new 10-day tool’ is still valid though not superior to the ‘PACTG-style tool’. However, there was no limit pre-set at the design level for a non-inferiority margin and based on recommendations from literature (EMA London, 27 July 2000.) it is normally inappropriate to set one after the study since this might introduce bias in establishing this limit. It was therefore not possible to prove that the ‘new 10-day tool’ was inferior to the control ‘PACTG-style tool’. Adherence levels produced by the ‘new 10-day tool’, however, are comparable both to the ‘PACTG-style tool’ in this study and to other self-report tools that have been used in similar settings in the southern African region and in the HIC and LMIC worldwide. This indicates that the

‘new 10-day tool’ is as accurate as its comparator and may be comparable to other self-report tools used among children on ART in the developed world (Albano et al. 2007, Martin et al. 2009), in sub-Saharan Africa (Vreeman et al. 2009) and in the southern African region (Reddi et al. 2007). However, a limited number of studies have explicitly employed techniques to reduce social desirability and recall bias and have yielded low adherence levels that are either closer to those measured by other methods (Bulgiba et al. 2013) or have specificity and sensitivity that are comparable (Godin, Gagné & Naccache 2003).

In my study, caregivers and children were informed that data collectors were not part of the healthcare providers who provide ART services at the health facilities and that adherence information for individuals would not be communicated to the health staff at the clinic. Even when given this assurance, reported non-adherence levels were very low. Despite similar measures to reduce social desirability bias being implemented in a Malaysian study conducted on adult patients on ART, self-reports had very low specificity and yet very high sensitivity versus therapeutic drug monitoring of individual ARVs (Bulgiba et al. 2013).

7.4.2 Concurrent validity of the ‘new 10-day tool’ against the MMAS-8

This study showed that the ‘new 10-day tool’, like its comparator, demonstrated concurrent validity by producing adherence levels that are related to those measured by the MMAS-8, another previously validated adherence monitoring tool (Morisky, Green & Levine 1986, Morisky et al. 2008). Higher scores on the MMAS-8 were found to be associated with taking 100% of doses using both caregiver- and child-reported ‘past-10 days’ and ‘past-7 days’ adherence levels. Similarly its comparator showed valid results when measured against this tool for ‘past-30 days’ child- and caregiver-reported adherence but could not show a relationship with the MMAS-8 scores for ‘past 7 days’ child reports.

Whereas it is expected that response bias could occur when caregivers reported adherence using both the ‘new 10-day tool’ and the MMAS-8 resulting in significant association between the two tools, the association between child reports using the ‘new 10-day tool’ and the caregiver reports using the MMAS-8 demonstrate that the two tools were both measuring what they should be measuring, denoting the validity of the tools as adherence measures. A previous study showed a high within-rater and inter-rater agreement among self-report methods (Farley et al. 2003a).

7.4.3 Inter-rater reliability of the ‘new 10-day tool’ between children and caregivers

Inter-rater reliability of adherence has been measured through agreement in adherence ratings on the same child over the same adherence assessment period between two different rating individuals. Older children in this study were partly responsible for taking their medication, with the caregiver ensuring that the child took his/her medication considering the daily commitments and duties of both child and caregiver. It also emerged during group discussions with children and caregivers that the caregiver did not always notice that the child had missed taking some doses, with the child often not disclosing this to the caregiver.

As the child grows older, caregivers tend to assume only partial responsibility for the child’s medication-taking and therefore may not be fully aware or informed of some incidences of missed doses. This may explain why children reported lower adherence levels than caregivers, hence affecting agreement between child- and caregiver-reported adherence which was only moderate, but significant, in this study. Dichotomised child-reported adherence at the 100% cut-off point was also significantly lower than that reported by adults at the longest adherence assessment periods of 10 days for the ‘new 10-day tool’. Similar differences were also observed for the comparator ‘PACTG-style tool’ for ‘past-14 days’ and ‘past-30 days’ at the 100% cut-off point, but the comparator tool had slightly lower agreement (fair agreement) between child and caregiver reports at the longest adherence assessment period of ‘past-30 days’, based on the classification of agreement specified by Landis (Landis, Koch 1977). The findings in my study concur with those from a review article by (Vreeman et al. 2008b) in which children reported generally lower adherence levels than their caregivers. Only rarely have studies shown that adherence levels do not differ between child and caregiver (Van Dyke et al. 2002).

7.5 The impact of adherence assessment period on reliability and validity of self-reports

Self-reported adherence was assessed over several adherence recall periods and across three adherence cut-off points to establish which recall periods and cut-off points are optimal for accurately measuring adherence. Although recall bias has been reported to be problematic over longer adherence assessment periods, longer recall periods of up to 30 days for self-reported adherence have been found to be optimal in assessing adherence, with over-reporting increasing with decreasing recall periods (Lu et al. 2008). My study found the lowest adherence levels at the longest adherence assessment periods of ‘past-10 days’ in the

experimental tool and ‘past-30 days’ in the control tool, and at the highest adherence cut-off point of 100%. Concurrent validity testing showed that, whereas ‘past-30 days’ child reports at the 100% cut-off point in the control group were associated with the MMAS-8, they were not associated with the MMAS-8 at ‘past-7 days’ recall period. Contrary to these findings, inter-rater agreement between children and caregivers was moderate for ‘past-7 days’ in both the experimental and control groups and moderate for ‘past-10 days’ adherence by the experimental tool. However, agreement was only fair (lower) for ‘past-30 days’ recall period. From these findings it appears that whereas validity of self-reports increases with increasing adherence recall periods, inter-rater reliability decreases. Shorter adherence periods have been noted to yield consistent but non-significantly higher adherence levels (Mannheimer et al. 2008).

7.6 Constructs of theoretical models and adherence

Constructs of theoretical models have been used to validate adherence monitoring tools. In a past adherence tool validation study, predictive validity of the MMAS-8 was assessed using social support, knowledge and attitudes (Morisky et al. 2008) with social support and knowledge both associated with medication adherence in hypertensive patients. In my study, we explored the relationship between total scores on items in these constructs and reported adherence in the experimental and control groups. Caregivers scored very high on beliefs about medicines, self-efficacy and ‘external’ factors but had low scores on social support. Nevertheless, among these constructs, only social support by the caregiver was found to be associated with adherence levels measured by the ‘new 10-day tool’, contrary to findings in a study conducted by Marhefka et al (2006a) where perceived social support was not associated with adherence, and none were associated with the comparator ‘PACTG-style tool’. It was noted during the group discussions with children and caregivers that family members and neighbours, when they have knowledge of the child’s HIV status and that the child is on ARVs, can take the role of reminding and ensuring that the child takes medication on time, especially when the caregiver is not at home. However, this is only possible when the caregiver and/or child have disclosed the child’s HIV status. According to the FGD results, disclosure can be hindered by perceptions of stigma. Those with perceptions of a society that stigmatises HIV-positive people may not disclose the HIV status of the child and hence the fact that the child is taking ART. The ‘new 10-day tool’ had the capacity to detect this link between social-support and adherence behaviour. However, there was no relationship

between adherence levels measured by the ‘new 10-day tool’ and other constructs of theoretical models that have been shown to influence adherence behaviour such as beliefs about medicines and self-efficacy, ART related knowledge and ‘external’ factors.

7.7 The feasibility and accuracy of the pill count method

The pill count method was routinely used in the two study sites to monitor adherence as an additional method to self-reported adherence. Pill counts have been found to be an unreliable measure of adherence and this measure has been shown to have no association with serum metabolite levels of the medication that is being taken (Appelgren et al. 2010). The method presents challenges in its accuracy and feasibility due to different aspects related to medication-handling behaviour of patients, including failure to bring medication containers to the health facility.

7.7.1 Availability of pill count data

Consistent with findings in previous studies (Appelgren et al. 2010, Farley et al. 2003a), a substantial proportion (99% and 40%) of the children in my study had not brought in medicine containers for all remaining pills for the two pill count methods, causing feasibility problems in using this method. A study from a different setting, however, reported a very high percentage (94%) of children returning their medication to the clinic for pill count assessment (Davies et al. 2008).

Whilst close to half of the children in my study had missing information for computing pill counts, including incomplete dispensing records, a study conducted among children on ART in the USA had a third (33.3%) of the pill counts with missing information due to reasons such as disposal of remaining pills before counting, forgetting to bring pills/empty containers to health facility, pills being at a home other than where the child is living, and sharing pills (Martin et al. 2009). Other challenges in the availability of pill count data in my study which have also been highlighted in the literature (Berg, Arnsten 2006) included availability of records on the quantity dispensed at the last refill and/or the date of refill, both of which are related to inadequate or inappropriate recording of information at the health facility. Similar to past research findings (Martin et al. 2009), both patient-related factors and healthcare facility-related factors can influence the quality of pill count data.

7.7.2 Accuracy of pill count method

For those who had adequate data on pill counts, challenges were noted with the accuracy of this method in assessing adherence. Whilst pill counts are normally referred to as a subjective measure of adherence, this study demonstrated that there was a lot of inconsistency in the quantity of returned medication. Two pill count methods were used in an effort to understand the circumstances surrounding the use of this method in the study settings. Additional to the ‘routine pill count’ method that takes into account only the amount of medication that is returned to the clinic, we used caregiver reports to establish whether there was any medication remaining at home at the previous dispensing, which, together with the amount dispensed at the previous visit, would contribute to the total amount of medication the patient had at the start of the adherence assessment period. This would not have been necessary if patients had brought in all remaining medication at each clinic visit and if the healthcare workers had collected all returned medication at each visit and had issued only enough supply to each patient for the next period before the review and refill visit.

It was noted that of the 126 participants who had complete information on the ‘routine pill count’ method, 59 (46.8%) managed to report on the number of tablets they had in their possession before receiving the supply for the adherence assessment period. This number, if not accounted for, has an effect of introducing error into the pill count method by lowering adherence levels. Including this amount into the pill count method provided an alternative method of computing pill count adherence that accounted for the caregiver reported residual quantity of pills at last refill; (‘Pill count RRQ’). Comparing the range of adherence levels between the two pill count methods shows that ‘Pill count RRQ’ had an effect of offsetting the negative adherence levels that were observed with the ‘routine pill count’ method. These negative pill count adherence levels arose from patients bringing in more pills than were dispensed at the start of the adherence assessment period, which was the last refill. Additional to offsetting the negative pill count adherence, the ‘Pill count RRQ’ method also increased calculated adherence levels at the 80%, 95% and 100% adherence cut-off points when compared to the ‘routine pill count’ method, although these differences were only significant at the 95% cut-off point.

It was apparent that using the pill count method to assess adherence in the study settings presents major challenges with only 3.2% and 5.1% bringing in the expected number of pills for 100% adherence, using both the ‘routine pill count’ method and ‘Pill count RRQ’,

respectively. The rest of the children had a discrepancy in the returned quantity of pills, with some bringing in more pills and others bringing in fewer pills than expected.

A substantial proportion of the study participants appeared to have ingested more pills than required, resulting in them having a shortfall in the quantity of returned medication. The shortfall may be an indication of either tampering with the remaining medication, keeping some supplies at home, sharing medication, pill dumping, or keeping medication in multiple locations (Appelgren et al. 2010).

As observed in my study, patients may bring in less medication than expected, giving rise to adherence levels above 100%. When this happens, researchers often allocate adherence of 100% to these patients, a practice known as ‘capping’ (Appelgren et al. 2010, Davies et al. 2008). In South Africa, 40.9% of children had adherence levels above 100%. In some programs patients may be given additional medication to last them a few more days beyond the next scheduled visit, to cushion them against non-adherence in the event that circumstantially they miss the scheduled visit by a day or two (Appelgren et al. 2010). This practice does not account for all shortfalls in returned medication since these patients could have been handling their medication inappropriately and may actually have been non-adherent. In our FGDs, we noted that some caregivers were keeping medication in multiple locations and alluded to a possibility that medication can be stolen, practices which could have resulted in patients returning fewer tablets to the clinic without necessarily consuming them.

Where health facilities have the practice of issuing a few extra tablets to last an additional two to three days, it is expected that there should be very small deviations in the quantity of returned medication from the expected quantity. In this case, the extent to which the returned quantity of medication varies from the expected, might be a better measure which points both to adherence and to pill handling behaviours, since it is difficult to ascertain what could have happened to the additional missing medication. Moreover, inappropriate medication-handling behaviours have been found to be associated with non-adherence behaviour. Failure to return remaining medication and pill containers at more than one clinic visit in the year was associated with lower adherence levels for those times when the pills are returned in a study conducted on adherence to ART among children in South Africa (Davies et al. 2008).

The percent discrepancy in returned medication is a measure that was found to be useful in determining the level to which children and caregivers were handling and administering medication in my study. With the 'routine pill count' method, the range for PD was 0-144. This finding, accompanied by negative adherence levels obtained from the 'routine pill count' method, indicate that some patients brought in more tablets than those dispensed at the previous visit, implying that patients might be keeping large amounts of tablets at home without bringing them to the health facility, or if they do, these are not accounted for by health workers during dispensing. However, most studies that have used the pill count method have not discussed the phenomenon of negative pill count adherence levels that were encountered in my study (Appelgren et al. 2010, Jasti et al. 2006, le Roux et al. 2009, Minzi, Naazneen 2008). Negative adherence levels were only observed with the 'routine pill count' method but not with the novel 'Pill count RRQ' method, a pill count method that included caregiver reports on quantity of medication that the child still had at previous dispensing. The high mean PD values (17%-19%) indicate that there are other factors involved in the discrepancy in pill counts beyond the issuing of an additional few days' supply. Veenstra et al (2010) documented on sharing or selling of ARV medications by patients in Zimbabwe during the economic crisis as patients tried to cope with inadequate drug supplies of the medications and or cope with the poor economic circumstances.

The practice of not returning all medication containers may affect routine monitoring of adherence in two ways. When patients leave some medication at home or in another location during one clinic visit, these patients may have adherence levels that are above 100% and if 'capping' is practiced, may be allocated to 100% adherence. However, when the same patients bring in this residual quantity of medication at their next clinic visit, pill count method may show that these patients have sub-optimal adherence levels. This is evidenced by a substantial number of caregivers who reported having this excess medication and hence an adjustment in pill count adherence using 'Pill count RRQ' resulting in raised adherence levels by this method. This shows that some of the apparent non-adherence may be due to excess medication being kept at home, as a result of non-adherence in the past or as a result of getting more supplies than required for the period, and may not necessarily reflect current non-adherence. Medication-handling behaviour therefore requires interventions for improvement as much as does adherence behaviour if adherence monitoring and subsequent interventions to improve adherence have to result in improved clinical outcomes.

Some of the challenges experienced in the use of clinic-based pill counts can be overcome by using unannounced home-based pill counts that have been found to be more accurate (Minzi, Naazneen 2008). Sensitivity of clinic-based pill counts against home-based pill counts was very low in a study conducted among children on ART in Uganda (Nabukeera-Barungi et al. 2007). However, even unannounced pill counts may have limitations in their accuracy as shown in studies where home-based pill counts were only associated with physicians' impression and electronic monitoring and not with antipsychotic blood levels and self-reports (Velligan et al. 2007). Unannounced pill count data among children on ART were incomplete for 26% of participants (Farley et al. 2008). Unannounced home-based pill counts cannot account for patients sharing medication or keep medication in multiple locations. In addition, this method demands more resources and additional staff to do the home visits, presenting potential challenges in settings that are already resource-constrained. Pill counts have been shown to underestimate the rate of omissions of medication doses compared to MEMS[®] (Svarstad et al. 1999). Regardless of these drawbacks, studies that have assessed adherence using both pill counts and self-reports have shown that pill counts correlate better with other objective methods than self-reports (Jasti et al. 2006).

7.7.3 Relationship between pill counts and reported adherence

PD for the 'routine pill count' had a significant association with child-reported adherence measured by the 'new 10-day tool' and child-reported adherence measured by the control 'PACTG-style tool', at 100% cut-off points. However these self-report measures had only fair agreements with capped adherence levels for 'routine pill count' at the 80% adherence cut-off point. These results are comparable to those found in other studies on adherence to ART in children in sub-Saharan Africa, but using caregiver reports. Caregiver-reported full adherence has been found to be associated with medication adherence in children on ART, but with only intermediate to poor agreement between self-reports and adherence measured by returned medicine (Davies et al. 2008, Nabukeera-Barungi et al. 2007).

Whilst the above studies have shown a significant relationship with adherence, in my study caregiver reports using the 'new 10-day tool' in the experimental group, the 'PACTG-style tool' in the control group and caregiver reports in combined groups using the MMAS-8 were not associated with pill count adherence, signifying poor concordance between caregiver reports and pill count data in this study.

This study showed that those children with a maximum score of 8 on the MMAS-8 score had a higher mean adherence by both pill count methods than did those children with a MMAS-8 score of <8, but these differences were not significant. Nevertheless, it cannot be concluded that the two measures are not associated since close to half (48.6%) of the children in this study did not have adequate data to compute 'routine pill count' adherence and therefore could not be included in this analysis, with further reduction in the sample size to only 24.1% of the study sample for 'Pill count RRQ'. The reduction in sample size for this analysis results in lowering of the statistical power and hence failure to show a statistically significant relationship where one may exist. Nevertheless, self-report measures are not always associated with non-self-report measures, with a review noting an association between the two measures in only 43% of the studies (Garber et al. 2004).

7.8 Factors associated with reported adherence and challenges to adherence

In this study, orphan status was associated with child-reported adherence, with orphans being 4.7 times more likely to be adherent. Contrary to this information, studies (Iroha et al. 2010, Reddi et al. 2007) have found no association between adherence levels and orphan status or found orphan status to be associated with non-adherence (Vreeman et al. 2008a, Wachholz, Ferreira 2007) However, there are multiple definitions of an orphan, with a study conducted in Kenya (Vreeman et al. 2009) defining an orphan as a child whose mother or both parents had died. In my study, where an orphan was defined as a child who had at least one parent (mother or father) who died, just above two thirds of the children were found to be orphans, a proportion similar to that observed in Kenya (Vreeman et al. 2008a) In my study, all other child demographic characteristics such as age, sex, type of usual residence and child's years of formal schooling were not associated with adherence. Past studies have shown conflicting information with regard to association between age and adherence, with younger age being less adherent (Bagenda et al. 2011), older age being less adherent (Hansudewechakul, Jourdain & Plangraun 2006) finding no association between child age and adherence (Reddi et al. 2007). However these studies have used adherence methods, adherence cut-off levels and age bands that are different from each other and from those employed in my study. Similar conflicting observations in my study and in past studies have been noted with regard to the association between the child's gender and adherence, (Martin et al. 2009).

Use of non-human reminders was, in my study, found to be associated with higher adherence levels with reminders other than humans being used in approximately three quarters of children. Davies et al (2008) reports that the main form of reminder was activities of daily living (40%). In my study, activities such as school going time and meal time were mentioned during the FGDs as being useful reminders for the morning and the evening doses respectively. About a quarter of those who use non-human reminders indicated that they use the alarm and, during discussions with children, it emerged that some children find it difficult to adhere since they do not have the watches or cell phones to inform them when it is time to take their medication. Whilst these appear to be a potentially useful adherence supporting tool, in a study conducted in an urban clinic in the USA, 15-22 year old youths reported forgetting to take medication as the main reason for missing doses despite mentioning that an alarm clock was the best aid for remembering to take doses and despite being given alarm watches as aids in remembering to take their medication (Lyon et al. 2003). The effectiveness of alarm watches or cell phones may be different in some of the rural settings where children have no other device to remind them or inform them when it is time to take medication and they have to use activities of daily living that do not follow a specific and strict schedule such as meal time. This practice of using such activities may result in 'interval' non-adherence.

The challenge of sticking to the required medication-taking intervals was also highlighted by children, and was ascribed to children leaving the home to perform economically-gainful activities and returning later than the time they are supposed to take their medication, resulting in interval non-adherence. Interval non-adherence was also mentioned by caregivers as resulting from children going elsewhere to play, but caregivers indicated that this challenge could be improved by disclosing to the child his or her HIV status and stressing the importance of adherence.

During the FGDs with children and caregivers, it emerged that the time the child goes to school acts as a reminder for the morning dose of ART, but quantitative data did not show that children attending school are more adherent than those out of school. School attendance, nevertheless, was very high among children in this study with almost 95% of children above the age of seven years attending formal school. Contrary to indications from discussions with parents and caregivers in my study, a past study conducted in Zambia showed that school attendance was associated with poorer adherence (Haberer et al. 2011).

At least one dedicated caregiver must be identified before initiating therapy in children. The national and international ART guidelines also encourage disclosure to another member of the household who will act as a secondary caregiver and recommend earliest possible disclosure of HIV status to the child whenever it is appropriate and feasible. Family support groups have been recommended as necessary to improve adherence. Disclosure of HIV status to child was more than double in my study (45%) than that reported in Kenya (Vreeman et al. 2010, Turissini et al. 2013). Caregivers in my study believed that disclosure to the child could have benefits such as improved ART adherence, especially in older children, but there lacked a consensus on the ideal age for disclosure, with caregivers suggesting age ranges of between six to 15 years depending on the maturity level of the child, signifying that disclosure is a gradual process which takes into account several factors (Marhefka et al. 2006a). Whilst caregivers associated disclosure with improved adherence, there were fears of negative consequences of disclosure to the child and disclosure to other people, findings similar to those observed by (Vreeman et al. 2010). Both perceptions of, and experienced stigma were reasons for this fear to disclose. Disclosure rates to older children (64% in children >7 years of age) were closer to those observed in Uganda (59% in children >8 years). There was also a significant positive association between disclosure of HIV status to the child, and both caregiver- and child-reported adherence levels for combined experimental and control groups, but this relationship was not significant in multivariate analysis. Again studies have shown conflicting information with regard to the relationship between disclosure and adherence to ART (Haberer et al. 2011, Marhefka et al. 2006a)

Although no socio-economic factors were associated with adherence in univariate analysis, discussions with children and caregivers revealed that both the children and their caregivers sometimes experience food shortages and lack of transport money to visit health facilities that results in them having to walk long distances. The economically-constrained environment for children on ART in Zimbabwe was also noted in a past study (Skovdal et al. 2011). Nevertheless Bagenda et al (2011) found that distance to the clinic was not associated with improved adherence. In Zambia, increased household income was associated with poorer adherence (Haberer et al. 2011) but in South Africa, access to water and electricity were associated with improved adherence (Davies et al. 2008).

Similar to observations made in Uganda (Nabukeera-Barungi et al. 2007), almost all (99.6%) the children were on first line regimens, mainly comprising stavudine, lamivudine and NVP.

Although studies have found regimen-related factors to affect adherence (Davies et al. 2008, Bagenda et al. 2011), none were found to be associated with adherence in my study. Similarly there was no indication that non-availability of medication at the health facility or at home had any substantial impact on adherence. Studies searched for reasons for children missing doses before the wide availability of ART and before public health facilities were offering ART services at no cost to the patient in resource-constrained settings, noted that shortage of drugs from pharmacies and lack of money to buy the medicines were among other reasons for missing doses (Mills et al. 2006, Weigel et al. 2009).

Among children who were cared for by a primary caregiver who was not a biological parent or sibling, those with a maternal relative as primary caregiver were found to be more adherent than those with a paternal primary caregiver, although there was no association between adherence and whether the primary caregiver was biological parent or not. No studies could be located that investigated this particular characteristic of primary caregivers. However, literature has shown conflicting findings on the relationship between the nature of the caregiver and adherence, with studies investigating different types of relationships (Bagenda et al. 2011, Hansudewechakul, Jourdain & Plangraun 2006, Jaspan et al. 2011, Martin et al. 2009). In my study and in another study conducted in Zimbabwe (Skovdal et al. 2011), it was noted that older children have increased roles in medication-taking and also take part in economic activities that improve the welfare of the family. This increased participation in daily activities may have an influence on the role of the primary caregiver in medication-taking; hence differences in findings that relate to the nature of the caregiver may also vary with the ages of the children, among their other socio-demographic characteristics. Similar to findings in my study, higher caregiver HIV prevalence (more than half) is reported in sub-Saharan Africa (Reddi et al. 2007) than in the USA (29%) (Martin et al. 2009), but in my study this factor was not found to influence adherence using caregiver or child reports. Similarly Martin et al (2009) did not find any association between caregiver HIV-status and adherence.

My study and several others did not show an association between educational status of caregiver and reported adherence (Bagenda et al. 2011, Martin et al. 2009, Marhefka et al. 2006a). Findings from the FGDs with children and caregivers in my study confirmed findings from a study by Mellins et al (2004) that worse parent-child communication can lead to non-adherence. However, there was no single item to measure this aspect since items the on child-

caregiver relationship were included in a composite scale of moderating factors that measured several aspects reflecting potential barriers to adherence outside child and caregiver characteristics.

Unavailability of ARV drugs, which has been cited in a study conducted among health workers as a major problem affecting HIV-infected children in Zimbabwe (Ferrand et al. 2010) and by Chimhuya, Nathoo and Rusakaniko (2012) as one of the causes for non-adherence, was not a major issue among children already on ART at my study sites. Although poor drug supply systems have been found to contribute to poor adherence (Minzi, Naazneen 2008) this was not the case in my study where almost all of the study participants reported that they had always been able to get their ARV drug supplies in time at the respective health facilities. This indicates that while there is a need for children to be initiated on ART nationally, the ART programs in the two study sites are doing well in matching the number of children they initiate on ART to the available ARV resources for sustainability of treatment in children and therefore non-availability of drugs cannot be a cause for non-adherence. The ART regimens were not very complex and the ARV pill burden was low for the majority of the children in my study, factors that could all lead to increased adherence.

From the FGDs conducted in my study, children and caregivers highlighted that adherence to ART among children, compared to adults, is further complicated by the need for both the caregiver and an older child to work together to effectively facilitate adherence, have a correct understanding of how the child is taking his/her medication and provide accurate reports of adherence behaviour to healthcare providers, with grandmother and non-biological primary caregivers being a common phenomenon among this child population on ART that has a far higher (68%) prevalence of orphanhood than in the general child population (16%) in Zimbabwe (UNAIDS 2010). A previous study conducted in Zimbabwe showed that caregivers felt that they were ill equipped to support children under their care (Mavhu et al. 2013).

7.9 Challenges to reporting adherence in children

From discussions with caregivers and children in my study, it appears that challenges in the accuracy of self-reports may demand more than merely the design of an improved tool, but may require that interventions be conducted to reduce barriers to reporting non-adherence.

This may be achieved by addressing factors that contribute to general negative perceptions of those who seek health services on the reaction of health providers to reporting non-adherence and that patient-healthcare provider relationship be improved. It emerged that some of the caregivers as well as the older children on ART avoid reporting non-adherence since they do not want to provoke the anger of health workers or convey the impression that they are irresponsible. Healthcare workers, therefore, have a role in improving the accuracy of reported adherence by creating a non-threatening atmosphere to those who report non-adherence. Improved healthcare-provider relationships may be instrumental in reducing social desirability bias in reported adherence.

Medication taking is a shared responsibility between the child and the caregiver. Older children in this study were partly responsible for taking their medication, in these circumstances the caregiver ensures that the child adheres to his/her medication regimen but this role is compromised considering the daily commitments and duties of both child and caregiver. Since the child and caregiver are not always together, it emerged during group discussions with children and caregivers that the caregiver did not always notice that the child had missed taking some doses, and that the child may not disclose this to the caregiver.

This partial responsibility for the child's medication-taking by the caregiver and hence lack of full knowledge on adherence behaviour may result in poor agreement between child reports and caregiver reports that have been observed in this study with children reporting lower adherence levels than their caregivers. Moreover, some children may pretend to have taken their dose of medication when asked to take this medication without direct observation, when in reality they have not swallowed the medication. In such instances, if the child owns up to this non-adherence behaviour at the health facility, the caregiver may unintentionally report higher adherence levels than those reported by the child resulting in poor agreement between child and caregiver reports.

In the absence of the caregiver, neighbours may take the role of reminding or ensuring that the child takes medication on time. This role, however, is only possible where the caregiver has disclosed the child's HIV status to the neighbour. It emerged during the discussions that caregivers and children who have perceptions of stigma may not disclose the child's HIV status to extended family members and neighbours. Nevertheless, it was not clear how this behaviour could affect reporting of adherence behaviour to the health care workers.

7.10 Methodological issues and study limitations

When evaluating an adherence tool, sensitivity, specificity and predictive values are normally used in the same population against either a gold standard or against biological markers (Farley et al. 2003b). Regardless of its drawbacks in assessing adherence (Martin et al. 2009), MEMS® has been used as a gold standard (Jasti et al. 2006) in evaluating adherence monitoring tools. The use of MEMS® is associated with extremely high costs (Martin et al. 2009, Müller et al. 2011), a factor that can limit its use not only in routine clinical use but in research conducted in resource-constrained settings. In my study which was conducted in a resource-constrained setting where MEMS® was unaffordable and viral loads measurements were not consistently and routinely taken, I used a superiority test against a frequently used self-report tool to test for the validity of the new self-report tool.

The use of a RCT design for my study was based on the assumption that any differences in adherence levels between the experimental ‘new 10-day tool’ and the control ‘PACTG-style tool’ are as a result of differences in specificity as opposed to differences in sensitivity of the tool, which have been found to be extremely high for self-reports. Self-report tools may not be 100% sensitive and hence the assumption may not completely hold.

In the study there was no non-inferiority margin pre-set at the design phase of this study and it is normally inappropriate to set one after the study since this might introduce bias in establishing this limit. This then implied that we could not establish whether the tool, although not shown to be superior, was non-inferior to the comparator ‘ACTG-style’ tool.

The study was limited to two sites in one African country and findings are therefore not readily generalizable to different settings in other countries. The sample-size for the RCT was calculated using the assumption that adherence levels by the ‘new 10-day tool’ would be approximately 25% below those of the existing tool, an assumption that was not met in this study, thus lowering the power of the study to detect a difference between the two tools, if any such difference truly exists.

The minimal sample size of 60 for child-reported adherence in each randomisation group was not reached. The conclusion that there was no relationship between the MMAS-8 and child

reports by the 'PACTG-style tool' cannot be made since the minimum sample size of 60 for child-reported adherence in each arm was not reached. Failure to reach the minimal sample size for child-reported adherence was mainly as a result of a substantial number of children ≥ 10 years either coming to the clinic unaccompanied by a caregiver or the caregiver coming for a refill of medication without the child, hence failing to meet the inclusion criteria.

Ideally the routine use of clinic-based pill count method in assessing adherence is done under the assumptions that clients bring in all medicine containers that they have at home each time they visit the clinic for medical review and refill of their medication. Staff at both study sites reported this to be the expected practice. In accordance with literature showing that this does not always happen in some settings (Martin et al. 2009), preliminary discussions with healthcare workers at the research sites revealed that staff were not certain how stringently this practice was followed at their health facilities.

Apart from patients bringing in all the medication containers and all the remaining medication to the health facility, the traditional pill count method reflects adherence levels accurately when patients do not share medication with others and do not keep medication in multiple places, which can result in less medication being returned to the clinic than would be expected for 100% adherence (Appelgren et al. 2010).

Additional to the above patient behaviours, an ideal pill counting environment requires that the health facility collects all returned medication at all visits and issues a supply that is just adequate until the next visit. Leaving some medication at home when visiting the clinic for prescription refill may result in more medication than expected being returned at the next refill visit, giving false non-adherence behaviour at the latter visit. There is also a need for the health facility to routinely record the quantity of medication issued in a regulated manner, with this information being easily accessible to those who conduct adherence monitoring by this method. If these conditions are not met, this poses challenges in relying on the pill count method to assess adherence.

Based on literature review (Martin et al. 2009, Appelgren et al. 2010) and the manner in which facilities at the research sites are designed to operate, pill counts are conducted when patients are required to bring in all their remaining medication with a fresh supply of medication being considered as the sole supply the patient has by the time they leave the

health facility. In my study sites, ‘routine pill counts’ were done by considering only the quantity of medication that were brought to the clinic and the quantity that was dispensed at the previous visit, assuming that there was no medication that remained at home at the previous dispensing (i.e. residual quantity at last refill). Under this assumption of no ‘residual quantity’ (RQ) of medication at last refill, the routine formula for pill count method (Appelgren et al. 2010, Martin et al. 2009) which in this thesis will be referred to as ‘routine pill count’, is:

$$\text{'Routine Pill count'} = \frac{\# \text{ of pills dispensed} - \# \text{ number of pills returned}}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100$$

This method is ideal in settings where the patient is asked to bring with them all remaining medication and compliance to this requirement is high, and where the healthcare workers remember to collect this medication before issuing the supply of the day. Since literature has shown that some patients still do not bring their remaining medication, presenting a challenge to this assumption (Appelgren et al. 2010, Martin et al. 2009) and in my study setting health staff expressed uncertainty of patient behaviour regarding this practice, it was deemed necessary to establish some alternative way of obtaining information on the remaining medication at last refill. There was no documented source of this quantity of medication remaining at last refill hence the use of caregiver reports on the quantity of remaining medication at last refill, which were not brought to the health facility, was explored and assessed. This provided a second method to calculate pill count adherence levels which would rely on caregiver-‘reported residual quantity’ (RRQ) of pills at the last refill (referred to as ‘Pill count RRQ’ in this study). In this study the formula that was used for pill count adherence levels using this second method is:

$$\text{'Pill count RRQ'} = \frac{(\# \text{ of pills dispensed} - \# \text{ number of pills returned}) + \text{residual quantity at last refill}}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100$$

From literature it was again noted that some patients share medicines whilst others simply do not bring all their remaining medication to the health facility and do not declare that they have left some medication at home or in other locations during routine adherence monitoring (Martin et al. 2009). This is bound to cause a shortfall in the quantity of medication returned to clinic (Appelgren et al. 2010). Whilst an excess of medication during pill count is interpreted as non-adherence indicating that this quantity of medication was not taken, in the

two pill count methods described above, a shortfall in expected quantity of medication is not distinguished from those who are 100% adherence. In their study on assessing the pill count methods of adherence monitoring, Appelgren et al (2010) classified those who brought in less medication than expected which would reflect adherence levels above 100%, as 100% adherent, a practice known as ‘capping’. Adherence levels of more than 100% can be a reflection of taking more medication than expected, which is still non-adherence, or can be a reflection of sharing and ‘hoarding’ medication, which are inappropriate medication-handling behaviours.

Since the patient medication-handling behaviours mentioned earlier in this section have been shown to result in an excess or a shortfall in medication returned to the clinic (Appelgren et al. 2010), a measure of assessing patient behaviour that combines both adherence and medication-handling behaviour was formulated for this study. The measure is the percent discrepancy in the quantity of returned medication, which is a measure of extent to which the medication returned to the clinic deviate from that expected at that visit, taking into account the period that has lapsed between dispensing and returning to clinic and ignoring whether the discrepancy is positive (more medication is returned) or negative (less medication is returned) a concept similar to that used in the calculation of percentage error. This measure can be taken to reflect the non-adherence rate regardless of the direction of the non-adherence behaviour (whether it reflects taking either more or less pills) or any pill handling behaviours that convey a false impression of these adherence behaviours.

The percent discrepancy in ‘Pill count RRQ’ was formulated as follows:

Percent discrepancy in ‘Pill count RRQ’

$$= 1 - \frac{|(\# \text{ of pills dispensed} - \# \text{ number of pills returned})| + \text{residual quantity at last refill}}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100$$

The corresponding percent discrepancy in ‘routine pill count’ method is given by the formula:

Percent discrepancy in ‘routine pill count’

$$= 1 - \frac{|(\# \text{ of pills dispensed} - \# \text{ number of pills returned})|}{\# \text{ of elapsed days between dispensing and returning date} \times \# \text{ of pills prescribed per day}} \times 100$$

Further complications in adherence monitoring and in comparing adherence levels across studies and populations arise from the different ways of evaluating adherence within each adherence monitoring method, with some studies utilizing mean adherence (Steele et al. 2001) as opposed to proportions adherent at a given cut-off point. Studies may report on adherence both as a continuous measure and as a dichotomous measure using several adherence cut-off points (Haberer et al. 2011). Mean pill count adherence levels were also presented. The challenge with mean adherence is that it does not provide the actual number of people that need interventions at critical adherence cut-off points. Mean adherence among a population provides a general view of adherence in the population whereas proportions of the population that are adherent at a given adherence cut-off point gives a more clinically useful view of how many children are in danger of developing treatment failure resulting from non-adherence.

CHAPTER 8: CONCLUSIONS

Adherence monitoring remains problematic, more so in resource constrained settings where self-reports and facility-based pill counts are widely used despite challenges associated with their use. Self-reports have low specificity, failing to detect a substantial number of non-adherent patients whereas almost all adherent patients are identified. My newly designed self-report tool did not produce adherence levels that are lower than those for a tool that uses the 'PACTG-style' questions despite the adoption of certain strategies when designing the tool. In general, past efforts to design self-reported adherence tools with higher sensitivity than current tools have not been successful and my research contributes to this body of evidence.

In the 'new 10-day tool', the use of visual cues of tablets and visual cues denoting the times at which the tablets are expected to be taken, as well as the verbal cues employed to provoke memory recall of respondents on their weekly activities in the 'past 10 days', were strategies that were unsuccessful in promoting recall of adherence behaviour within this period. The strategy of encouraging the respondent to actively participate in the shading of pictorials representing tablets not taken, as a way of bringing him/her to engage his/her mind into reflecting on and reporting past adherence behaviour more accurately, did not generate positive outcomes.

It was apparent from FGDs with children and caregivers that the major challenge in reporting non-adherence to the service providers was more likely to be caused by social desirability than by recall bias. In this regard the patient- or caregiver-provider relationship appears to be an important factor in determining whether any non-adherence by the child will be reported. Perceptions of the child or caregiver regarding the healthcare provider's response to reporting of non-adherence behaviour were demonstrated to be crucial for accurate reporting of non-adherence. When patients or caregivers perceive that reporting of non-adherence will not be acceptable and that they may be viewed as irresponsible, they may try and avoid giving such reports despite missing some medication doses.

A further barrier to reporting non-adherence is caregiver ignorance of the fact that the child missed some doses. This happens mainly when the child is older and assumes more responsibility for their medication-taking whereas the caregiver's role during this same time reduces. The caregiver may believe the child when the child reports having taken the

medication. Child-caregiver relationships are also crucial since a child may intentionally fail to disclose non-adherence to the caregiver. This discrepancy between the child and caregiver of knowledge of the child's non-adherence behaviour can lead to poor agreement between the subsequent reporting of the behaviour at the health facility, and possibly explains caregivers reporting higher adherence levels than children.

Findings from focus group discussions with parents and caregivers confirm that social-desirability bias patient-provider relationships and the child-caregiver relationships and nature of collaboration in medication-taking play a critical role in the accuracy of reported adherence, probably more than recall bias hence interventions to improve these relationships may be valuable in improving the accuracy of self-reports than designing new tools.

Study caregiver-reported adherence levels of 95.8% for 'past 30 days' at 95% cut-off point, were comparable to those observed in a different study conducted at one of the study sites approximately a year later (92.6%). Full (100%) adherence as reported by caregivers fell within the range of 89% - 98%, similar to adherence levels previously reported in both sub-Saharan Africa and HIC.

Whilst the 'new 10-day tool' was not shown to be superior to the 'PACTG-style tool', this new tool was shown to be a valid adherence monitoring tool with adherence levels that were comparable to those of the 'PACTG-style tool'. The new tool was also shown to have a significant relationship with a previously validated MMAS-8 scale and was found to be reliable, showing significant but moderate agreement between child and caregiver reports. Additional to this, the new tool was associated with social support scores whilst the control tool was not. Adherence levels were lowest at longest adherence assessment periods of 'past 14 days' in the experimental group and 'past 30 days' in the control group indicating that results generated from the longer adherence assessment periods are more likely to show higher specificity for adherence behaviour.

Contrary to the congruence established between my self-reported adherence results and those from other studies, clinic pill counts in my study were markedly different from previous reports. At the 95% cut-off point, pill count adherence levels of 39% for 'routine pill count' and 58% for 'Pill count RRQ', respectively, were lower than those reported in a later study in

Zimbabwe (81%) as well as in most studies conducted in HIC and sub-Saharan Africa, but were comparable to some unannounced home pill count adherence levels.

The pill count method showed some feasibility issues with only about half of the children having adequate data to compute pill counts. For those who had data on pill counts, only very few returned the right amount of medication to reflect 100% adherence, whereas the majority returned more medication than expected, implying less than 100% adherence. These findings demonstrate the possibility of identifying non-adherence behaviour reflected in this pill count information together with adherence reports during interviews and information collected through FGDs. However, there are additional problems associated with medication-handling and/or the issuing of medication at the health facility, resulting in children returning less medication than prescribed.

In univariate analysis, child-reported adherence in my study was associated with a different set of factors from those associated with caregiver-reported adherence, although a few were common to both. In multivariate analysis, there were no factors identified that were common to both self-reported adherence methods. Child reports identified orphanhood as a predictor of adherence behaviour whereas having a maternal primary caregiver, using another reminder other than people alone, and having knowledge of dosing frequency, were all associated with adherence by caregiver reports. My study showed that different adherence methods may not be associated with the same factors, implying potential reliability issues across different methods. My study has, like other studies, shown conflicting information on factors influencing adherence demonstrating that the nature of identified factors may be context specific and is subject to the bias introduced by the reliability levels of the adherence measurement tool.

In conclusion, the tool developed in my study is a valid and reliable tool with a potential of identifying constructs of theoretical models that influence behaviour and hence provide aspects that can be targeted for interventions. The comparisons between the new tool and its control, however, reveals challenges in designing adherence monitoring tools and in assessing adherence in the study settings. My study contributes to the understanding of issues in reporting non-adherence and the causes of discrepancy in child and caregiver reports. This deeper understanding of adherence issues can be applied in informing future interventions

aiming to improve the accurate reporting of non-adherence and can inform approaches and emphasis on adherence counselling.

My study also confirms prior observations that the pill count method has feasibility issues associated with caregivers returning medication containers to the health facilities, the need to improve handling of medication by children and caregivers, and the need to improve the accuracy of recording of information required for computing pill count adherence by the health facility.

8.1 Recommendations for practice

Healthcare providers must record complete dispensing information such as date of dispensing and quantity of each medication in order to facilitate the computing of pill count adherence levels. The information should be recorded on documents that are easily accessible to those who conduct pill counts and calculate adherence levels. Past dispensing history is useful in understanding the source of any excess medication returned at a visit, or any shortfalls in the returned medication, hence continuity of such records is essential in improving the accuracy of this adherence monitoring method. Percent discrepancy is useful in determining child cases that have larger discrepancies in pill counts and hence require intervention for both adherence behaviour and medication-handling behaviours since medication-handling behaviour requires interventions for improvement as much as does adherence behaviour if adherence monitoring and subsequent interventions to improve adherence have to result in improved clinical outcomes.

Healthcare providers must be trained and encouraged to recognise that reliance on self-reported adherence in monitoring patients on ART requires that these reports should be accurate. Therefore every effort must be applied to creating an environment that minimises barriers to adherence, such as provider anger or judgemental attitudes, and encourages patients to report non-adherence behaviour.

8.2 Recommendations for further research

Further research should focus on designing and testing a pill count adherence tool that enables the clear, continuous recording of information required for computing pill count

adherence data without creating much additional workload to healthcare staff in resource constrained settings. Identification of causes of both shortfalls as well as excesses in pill counts in medication returned to the health facility should be researched in settings similar to those for my study.

The quality of the patient-provider relationship demands further research in Africa, as although this has been extensively explored in HIC, little has emanated from poorly resourced healthcare settings in LMIC. This research should investigate barriers and facilitators to open, two-way communication in an attempt to improve the accuracy of self-report methods.

Predictive validity and concurrent validity of the ‘new 10-day tool’ based on associations with viral load and MEMS®, respectively, should be explored. Age differences in reliability and validity may be present and could suggest differential recommendations for assessments between children and adolescents. Barriers to adherence could be explored in a mixed-methods design, triangulating qualitative and quantitative data since this study assessed these using only qualitative methods.

REFERENCES

- Akobeng, A.K. 2007, "Understanding diagnostic tests 1: sensitivity, specificity and predictive values", *Acta Paediatrica*, vol. 96, no. 3, pp. 338-341.
- Albano, F., Giacomet, V., De Marco, G., Bruzzese, E., Starace, F. & Guarino, A. 2007, "Adherence to antiretroviral therapy in children: A comparative evaluation of caregiver reports and physician judgement", *AIDS Care*, vol. 19, no. 6, pp. 764-766.
- Amico, K.R., Fisher, W.A., Cornman, D.H., Shuper, P.A., Redding, C.G., Konkle-Parker, D.J., Barta, W. & Fisher, J.D. 2006, "Visual analog scale of ART adherence: association with 3-day self-report and adherence barriers", *Journal of Acquired Immune Deficiency Syndromes*, vol. 42, no. 4, pp. 455-459.
- Amico, K.R., Mansoor, L.E., Cornelia, A., Torjesen, K. & van der Straten, A. 2013, "Adherence support approaches in biomedical HIV prevention trials: Experiences, insights and future directions from four multisite prevention trials", *AIDS and Behavior*, vol. 17, no. 6, pp.2143-2155.
- Appelgren, K.E., Nietert, P.J., Hulsey, T.C., Hollis, B.W. & Wagner, C.L. 2010, "Analyzing adherence to prenatal supplement: does pill count measure up?", *International Journal of Endocrinology*, 2010: 631971. Published online 2010 February 4. doi: 10.1155/2010/631971
- Arnsten, J.H., Demas, P.A., Grant, R.W., Gourevitch, M.N., Farzadegan, H., Howard, A.A. & Schoenbaum, E.E. 2002, "Impact of Active Drug Use on Antiretroviral Therapy Adherence and Viral Suppression in HIV-infected Drug Users", *Journal of General Internal Medicine*, vol. 17, no. 5, pp. 377-381.
- Aronson, J.K. 2007, "Compliance, concordance, adherence", *British Journal of Clinical Pharmacology*, vol. 63, no. 4, pp. 383-384.
- ARROW Trial team. 2013, "Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial.", *Lancet*, vol. 381, no. 9875, pp. 1391–1403.
- Assembly, U.G. 2001, "Declaration of commitment on HIV/AIDS: Global crisis–global action", *UN Special Session on HIV/AIDS, 25-27 June 2001, New York*, .
- Assembly, U.G. 2000, "United Nations Millennium Declaration", *resolution adopted*, vol. 18.
- Back, D., Gibbons, S. & Khoo, S. 2006, "An update on therapeutic drug monitoring for antiretroviral drugs", *Therapeutic Drug Monitoring*, vol. 28, no. 3, pp. 468-473.
- Bagenda, A., Barlow-Mosha, L., Bagenda, D., Sakwa, R., Fowler, M.G. & Musoke, P.M. 2011, "Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda", *Annals of Tropical Paediatrics*, vol. 31, no. 3, pp. 235-245.

- Balikuddembe, R., Kayiwa, J., Musoke, D., Ntale, M., Baveewo, S., Waako, P. & Obua, C. 2012, "Plasma drug level validates self-reported adherence but predicts limited specificity for nonadherence to antiretroviral therapy", *ISRN Pharmacology*, , 2012: 274978. Published online 2012 March 6. doi: [10.5402/2012/274978](https://doi.org/10.5402/2012/274978)
- Bandura, A. 1989, "Human agency in social cognitive theory.", *American Psychologist*, vol. 44, no. 9, pp. 1175-1184.
- Bangsberg, D.R. 2006, "Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression", *Clinical Infectious Diseases*, vol. 43, no. 7, pp. 939-941.
- Bangsberg, D.R., Bronstone, A., Chesney, M.A. & Hecht, F.M. 2002, "Computer-assisted self-interviewing (CASI) to improve provider assessment of adherence in routine clinical practice", *Journal of Acquired Immune Deficiency Syndromes*, vol. 31, pp. S107-S111.
- Bangsberg, D.R., Perry, S., Charlebois, E.D., Clark, R.A., Roberston, M., Zolopa, A.R. & Moss, A. 2001, "Non-adherence to highly active antiretroviral therapy predicts progression to AIDS", *Aids*, vol. 15, no. 9, pp. 1181-1183.
- Banning, M. 2012, "Adherence to adjuvant therapy in post-menopausal breast cancer patients: a review", *European Journal of Cancer Care*, vol. 21, no. 1, pp. 10-19.
- Bärnighausen, T., Chaiyachati, K., Chimbindi, N., Peoples, A., Haberer, J. & Newell, M. 2011, "Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies", *The Lancet Infectious Diseases*, vol. 11, no. 12, pp. 942-951.
- Beach, M.C., Keruly, J. & Moore, R.D. 2006, "Is the Quality of the Patient-Provider Relationship Associated with Better Adherence and Health Outcomes for Patients with HIV?", *Journal of General Internal Medicine*, vol. 21, no. 6, pp. 661-665.
- Becker, M.H., Radius, S.M., Rosenstock, I.M., Drachman, R.H., Schuberth, K.C. & Teets, K.C. 1978, "Compliance with a medical regimen for asthma: a test of the health belief model.", *Public Health Reports*, vol. 93, no. 3, pp. 268.
- Bell, J.S., Airaksinen, M.S., Lyles, A., Chen, T.F. & Aslani, P. 2007, "Concordance is not synonymous with compliance or adherence", *British Journal of Clinical Pharmacology*, vol. 64, no. 5, pp. 710-711.
- Berg, K.M. & Arnsten, J.H. 2006, "Practical and conceptual challenges in measuring antiretroviral adherence", *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, no. Suppl 1, pp. S79-S87.
- Bhaskaran, K., Hamouda, O., Sannes, M., Boufassa, F., Johnson, A.M., Lambert, P.C. & Porter, K. 2008, "Changes in the risk of death after HIV seroconversion compared with mortality in the general population", *The Journal of the American Medical Association*, vol. 300, no. 1, pp. 51-59.

- Bhattacharya, M. & Dubey, A.P. 2011, "Adherence to antiretroviral therapy and its correlates among HIV-infected children at an HIV clinic in New Delhi", *Annals of Tropical Paediatrics*, vol. 31, no. 4, pp. 331-337.
- Birdthistle, I.J., Floyd, S., Machingura, A., Mudziwapasi, N., Gregson, S. & Glynn, J.R. 2008, "From affected to infected? Orphanhood and HIV risk among female adolescents in urban Zimbabwe", *AIDS*, vol. 22, no. 6, pp. 759-766.
- Biressaw, S., Abegaz, W.E., Abebe, M., Taye, W.A. & Belay, M. 2013, "Adherence to Antiretroviral Therapy and associated factors among HIV infected children in Ethiopia: unannounced home-based pill count versus caregivers' report", *BMC Pediatrics*, vol. 13, no. 1, pp. 132.
- Bisson, G.P., Gross, R., Bellamy, S., Chittams, J., Hislop, M., Regensberg, L., Frank, I., Maartens, G. & Nachega, J.B. 2008, "Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy", *PLoS Medicine*, vol. 5, no. 5, pp. e109.
- Blanco, J.M.S., Pérez, I.R. & March, J.C. 2005, "Adherence to antiretroviral therapy among HIV-infected prison inmates (Spain)", *International Journal of STD & AIDS*, vol. 16, no. 2, pp. 133-138.
- Boutron, I., Moher, D., Altman, D.G., Schulz, K.F. & Ravaud, P. 2008, "Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration", *Annals of Internal Medicine*, vol. 148, no. 4, pp. 295-309.
- Breton, G., Lewden, C., Spire, B., Salmon, D., Brun-Vézinet, F., Duong, M., Allavena, C., Leport, C. & Salamon, R. 2007, "Characteristics and response to antiretroviral therapy of HIV-1-infected patients born in Africa and living in France", *HIV Medicine*, vol. 8, no. 3, pp. 164-170.
- Brian Haynes, R., Ann McKibbin, K. & Kanani, R. 1996, "Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications", *The Lancet*, vol. 348, no. 9024, pp. 383-386.
- Buchmann, W.F. 1997, "Adherence: a matter of self-efficacy and power", *Journal of Advanced Nursing*, vol. 26, no. 1, pp. 132-137.
- Bulgiba, A., Mohammed, U.Y., Chik, Z., Lee, C. & Peramalah, D. 2013, "How well does self-reported adherence fare compared to therapeutic drug monitoring in HAART?", *Preventive Medicine*, vol. 57, supplement, pp. S34-S36.
- Butler, J.A., Peveler, R.C., Roderick, P., Horne, R. & Mason, J.C. 2004, "Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring", *Transplantation*, vol. 77, no. 5, pp. 786-789.
- Byerly, M.J., Nakonezny, P.A. & Rush, A.J. 2008, "The Brief Adherence Rating Scale (BARS) validated against electronic monitoring in assessing the antipsychotic medication adherence of outpatients with schizophrenia and schizoaffective disorder", *Schizophrenia Research*, vol. 100, no. 1, pp. 60-69.

- Campbell, C., Skovdal, M., Mupambireyi, Z., Madanhire, C., Nyamukapa, C. & Gregson, S. 2012, "Building adherence-competent communities: Factors promoting children's adherence to anti-retroviral HIV/AIDS treatment in rural Zimbabwe", *Health & Place*, vol. 18, no. 2, pp. 123-131.
- Cerkoney, K.A.B. & Hart, L.K. 1980, "The relationship between the health belief model and compliance of persons with diabetes mellitus", *Diabetes Care*, vol. 3, no. 5, pp. 594-598.
- Chacko, L., Ford, N., Sbaiti, M. & Siddiqui, R. 2012, "Adherence to HIV post-exposure prophylaxis in victims of sexual assault: a systematic review and meta-analysis", *Sexually Transmitted Infections*, vol. 88, no. 5, pp. 335-341.
- Chan, Y. 2003, "Randomised Controlled Trials (RCTs)-Sample Size: The Magic Number?", *Singapore Medical Journal*, vol. 44, no. 4, pp. 172-174.
- Chasela, C.S., Hudgens, M.G., Jamieson, D.J., Kayira, D., Hosseinipour, M.C., Kourtis, A.P., Martinson, F., Tegha, G., Knight, R.J. & Ahmed, Y.I. 2010, "Maternal or infant antiretroviral drugs to reduce HIV-1 transmission", *New England Journal of Medicine*, vol. 362, no. 24, pp. 2271-2281.
- Chesney, M.A., Ickovics, J., Chambers, D., Gifford, A., Neidig, J., Zwickl, B., Wu, A. & patient care committee & adherence working group of the outcomes committee of the adult aids clinical trials group (AACTG) 2000, "Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments", *AIDS Care*, vol. 12, no. 3, pp. 255-266.
- Chigwedere, P., Seage III, G.R., Lee, T. & Essex, M. 2008, "Efficacy of antiretroviral drugs in reducing mother-to-child transmission of HIV in Africa: a meta-analysis of published clinical trials", *AIDS Research and Human Retroviruses*, vol. 24, no. 6, pp. 827-837.
- Chima, I. 2007, *National Paediatric ART Site Survey 2007*, Chima, I. (2007). National Paediatric ART Site Survey 2007, Zimbabwe Ministry of Health and Child Welfare, Elizabeth Glaser Paediatric AIDS Foundation., Harare.
- Chimhuya, S., Nathoo, K. & Rusakaniko, S. 2012, *Non-adherence to highly active antiretroviral therapy in children attending HIV treatment clinic at Harare Children's Hospital-Zimbabwe*. Central African Journal of Medicine, *in press*.
- Chiu, C., Kuo, M., Yu, S., Su, B.Y. & Cheng, T. 2013, "Adherence to osteoporosis regimens among men and analysis of risk factors of poor compliance: a 2-year analytical review", *BMC Musculoskeletal Disorders*, vol. 14, no. 1, pp. 276.
- Choo, P.W., Rand, C.S., Inui, T.S., Lee, M.T., Cain, E., Cordeiro-Breault, M., Canning, C. & Platt, R. 1999, "Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy", *Medical Care*, vol. 37, no. 9, pp. 846-857.
- Christensen, E. 2007, "Methodology of superiority vs. equivalence trials and non-inferiority trials", *Journal of Hepatology*, vol. 46, no. 5, pp. 947-954.

- Ciaranello, A.L., Perez, F., Engelsmann, B., Walensky, R.P., Mushavi, A., Rusibamayila, A., Keatinge, J., Park, J., Maruva, M. & Cerda, R. 2013, "Cost-effectiveness of World Health Organization 2010 guidelines for prevention of mother-to-child HIV transmission in Zimbabwe", *Clinical Infectious Diseases*, vol. 56, no. 3, pp. 430-446.
- Collier, A.C., Ribaud, H., Mukherjee, A.L., Feinberg, J., Fischl, M.A. & Chesney, M. 2005, "A Randomized Study of Serial Telephone Call Support to Increase Adherence and Thereby Improve Virologic Outcome in Persons Initiating Antiretroviral Therapy", *Journal of Infectious Diseases*, vol. 192, no. 8, pp. 1398-1406.
- Conn, K.M., Halterman, J.S., Fisher, S.G., Yoos, H.L., Chin, N.P. & Szilagyi, P.G. 2005, "Parental beliefs about medications and medication adherence among urban children with asthma", *Ambulatory Pediatrics*, vol. 5, no. 5, pp. 306-310.
- Costa, L.S., Latorre, Maria do Rosário Dias de, Silva, M.H.d., Bertolini, D.V., Machado, D.M., Pimentel, S.R. & Marques, Heloísa Helena de Sousa 2008, "Validity and reliability of a self-efficacy expectancy scale for adherence to antiretroviral therapy for parents and carers of children and adolescents with HIV/AIDS", *Jornal de Pediatria*, vol. 84, no. 1, pp. 41-46.
- Coutsoudis, A., Pillay, K., Kuhn, L., Spooner, E., Tsai, W. & Coovadia, H.M. 2001, "Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa", *AIDS*, vol. 15, no. 3, pp. 379-387.
- D'Agostino, R.B., Massaro, J.M. & Sullivan, L.M. 2003, "Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics", *Statistics in Medicine*, vol. 22, no. 2, pp. 169-186.
- Davies, M., Boule, A., Fakir, T., Nuttall, J. & Eley, B. 2008, "Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study", *BMC Pediatrics*, vol. 8, no. 1, pp. 34.
- Davies, M., Moultrie, H., Eley, B., Rabie, H., Van Cutsem, G., Giddy, J., Wood, R., Technau, K., Keiser, O. & Egger, M. 2011, "Virologic failure and second-line antiretroviral therapy in children in South Africa-The IeDEA Southern Africa Collaboration", *Journal of Acquired Immune Deficiency Syndromes (1999)*, vol. 56, no. 3, pp. 270.
- de Castella, T. 2003, "Health workers struggle to provide care in Zimbabwe", *The Lancet*, vol. 362, no. 9377, pp. 46-47.
- Denhaerynck, K., Schäfer-Keller, P., Young, J., Steiger, J., Bock, A. & De Geest, S. 2008, "Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant patients", *BMC Medical Research Methodology*, vol. 8, no. 1, pp. 5.
- Denny, T., Yogev, R., Gelman, R., Skuza, C., Oleske, J., Chadwick, E., Cheng, S. & Connor, E. 1992, "Lymphocyte subsets in healthy children during the first 5 years of life", *The Journal of the American Medical Association*, vol. 267, no. 11, pp. 1484-1488.

- Deschamps, A.E., De Geest, S., Vandamme, A., Bobbaers, H., Peetermans, W.E. & Wijngaerden, E.V. 2008, "Diagnostic value of different adherence measures using electronic monitoring and virologic failure as reference standards", *AIDS Patient Care and STDs*, vol. 22, no. 9, pp. 735-743.
- DiMatteo, M.R. 2004, "Social support and patient adherence to medical treatment: a meta-analysis.", *Health Psychology*, vol. 23, no. 2, pp. 207.
- Duong, M., Piroth, L., Peytavin, G., Forte, F., Kohli, E., Grappin, M., Buisson, M., Chavanet, P. & Portier, H. 2001, "Value of patient self-report and plasma human immunodeficiency virus protease inhibitor level as markers of adherence to antiretroviral therapy: relationship to virologic response", *Clinical Infectious Diseases*, vol. 33, no. 3, pp. 386-392.
- Edwards, L.V. 2006, "Perceived social support and HIV/AIDS medication adherence among African American women", *Qualitative Health Research*, vol. 16, no. 5, pp. 679-691.
- Elise, A., France, A.M., Louise, W.M., Bata, D., François, R., Roger, S. & Philippe, M. 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 Syndromes*, vol. 40, no. 4, pp. 498-500.
- Ellis, D.A., Naar-King, S., Cunningham, P.B. & Secord, E. 2006, "Use of multisystemic therapy to improve antiretroviral adherence and health outcomes in HIV-infected pediatric patients: evaluation of a pilot program", *AIDS Patient Care & STDs*, vol. 20, no. 2, pp. 112-121.
- EMA London, 27 July 2000., *Points to consider on switching between superiority and non-inferiority*.
- Farley, J.J., Montepiedra, G., Storm, D., Sirois, P.A., Malee, K., Garvie, P., Kammerer, B., Naar-King, S. & Nichols, S. 2008, "Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count", *Journal of Developmental & Behavioral Pediatrics*, vol. 29, no. 5, pp. 377-384.
- Farley, J., Hines, S., Musk, A., Ferrus, S. & Tepper, V. 2003a, "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 Syndromes*, vol. 33, no. 2, pp. 212-218.
- Farley, J., Hines, S., Musk, A., Ferrus, S. & Tepper, V. 2003b, "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 Syndromes*, vol. 33, no. 2, pp. 211.
- Ferrand, R., Lowe, S., Whande, B., Munaiwa, L., Langhaug, L., Cowan, F., Mugurungi, O., Gibb, D., Munyati, S., Williams, B.G. & Corbett, E.L. 2010, "Survey of children accessing HIV services in a high prevalence setting: time for adolescents to count?", *Bulletin of the World Health Organization*, vol. 88, no. 6, pp. 428-434.

- Fetzer, B.C., Mupenda, B., Lusiana, J., Kitetele, F., Golin, C. & Behets, F. 2011, "Barriers to and Facilitators of Adherence to Pediatric Antiretroviral Therapy in a Sub-Saharan Setting: Insights from a Qualitative Study", *AIDS Patient Care & STDs*, vol. 25, no. 10, pp. 611-621.
- Fidder, H.H., Singendonk, M.M., van der Have, M., Oldenburg, B. & van Oijen, M.G. 2013, "Low rates of adherence for tumor necrosis factor- α inhibitors in Crohn's disease and rheumatoid arthritis: Results of a systematic review", *World Journal of Gastroenterology: WJG*, vol. 19, no. 27, pp. 4344.
- Fielding, D. & Duff, A. 1999, "Compliance with treatment protocols: interventions for children with chronic illness", *Archives of Disease in Childhood*, vol. 80, no. 2, pp. 196-200.
- Fishbein, M. & Ajzen, I. 1975, *Belief, attitude, intention and behavior: An introduction to theory and research*. Reading, MA: Addison-Wesley.
- Folch-Lyon, E. & Trost, J.F. 1981, "Conducting focus group sessions", *Studies in Family Planning*, vol. 12, no. 2, pp. 443-449.
- Ford, N., Darder, M., Spelman, T., Maclean, E., Mills, E. & Boulle, A. 2010, "Early Adherence to Antiretroviral Medication as a Predictor of Long-Term HIV Virological Suppression: Five-Year Follow Up of an Observational Cohort", *PLoS ONE*, vol. 5, no. 5, pp. 1-4.
- Gagné, C. & Godin, G. 2005, "Improving self-report measures of non-adherence to HIV medications", *Psychology and Health*, vol. 20, no. 6, pp. 803-816.
- Garay-Sevilla, M.E., Nava, L.E., Malacara, J.M., Huerta, R., de León, J.D., Mena, A. & Fajardo, M.E. 1995, "Adherence to treatment and social support in patients with non-insulin dependent diabetes mellitus", *Journal of Diabetes and its Complications*, vol. 9, no. 2, pp. 81-86.
- Garber, M.C., Nau, D.P., Erickson, S.R., Aikens, J.E. & Lawrence, J.B. 2004, "The concordance of self-report with other measures of medication adherence: a summary of the literature", *Medical Care*, vol. 42, no. 7, pp. 649-652.
- Garfield, S., Clifford, S., Eliasson, L., Barber, N. & Willson, A. 2011, "Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review", *BMC Medical Research Methodology*, vol. 11, no. 1, pp. 149.
- Gatti, M.E., Jacobson, K.L., Gazmararian, J.A., Schmotzer, B. & Kripalani, S. 2009, "Relationships between beliefs about medications and adherence", *American Journal of Health-System Pharmacy*, vol. 66, no. 7, pp. 657-664.
- Giacomet, V., Albano, F., Starace, F., de Franciscis, A., Giaquinto, C., Gattinara, G.C., Bruzzese, E., Gabiano, C., Galli, L., Vigano, A., Caselli, D. & Guarino, A. 2003, "Adherence to antiretroviral therapy and its determinants in children with human immunodeficiency virus infection: a multicentre, national study", *Acta Paediatrica*, vol. 92, no. 12, pp. 1398-1402.

- Gibb, D.M., Goodall, R.L., Giacomet, V., Mcgee, L., Compagnucci, A. & Lyall, H. 2003, "Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial", *The Pediatric Infectious Disease Journal*, vol. 22, no. 1, pp. 56-62.
- Gillespie, S., Norman, A. & Finley, B. 2005, "Child vulnerability and HIV/AIDS in sub-Saharan Africa: What we know and what can be done", *International Food Policy Research Institute*) Amy Norman University of Calgary, Canada Betsy Finley, Tulane University, USA, .
- Giordano, T.P., Guzman, D., Clark, R., Charlebois, E. & Bangsberg, D. 2004, "Measuring adherence to antiretroviral therapy in a diverse population using a visual analogue scale", *HIV Clinical Trials*, vol. 5, pp. 74-79.
- Glass, T.R., De Geest, S., Hirschel, B., Battegay, M., Furrer, H., Covassini, M., Vernazza, P.L., Bernasconi, E., Rickenboch, M. & Weber, R. 2008, "Self-reported non-adherence to antiretroviral therapy repeatedly assessed by two questions predicts treatment failure in virologically suppressed patients", *Antiviral Therapy*, vol. 13, no. 1, pp. 77.
- Godin, G., Gagné, C. & Naccache, H. 2003, "Validation of a self-reported questionnaire assessing adherence to antiretroviral medication", *AIDS Patient Care and STDs*, vol. 17, no. 7, pp. 325-332.
- Gonzalez, J.S., Penedo, F.J., Antoni, M.H., Durán, R.E., McPherson-Baker, S., Ironson, G., Isabel Fernandez, M., Klimas, N.G., Fletcher, M.A. & Schneiderman, N. 2004, "Social support, positive states of mind, and HIV treatment adherence in men and women living with HIV/AIDS.", *Health Psychology*, vol. 23, no. 4, pp. 413.
- Goulder, P.J., Jeena, P., Tudor-Williams, G. & Burchett, S. 2001, "Paediatric HIV infection: correlates of protective immunity and global perspectives in prevention and management", *British Medical Bulletin*, vol. 58, no. 1, pp. 89-108.
- Gozum, S. & Hacıhasanoglu, R. 2009, "Reliability and validity of the Turkish adaptation of medication adherence self-efficacy scale in hypertensive patients", *European Journal of Cardiovascular Nursing*, vol. 8, no. 2, pp. 129-136.
- Graves, M.M., Roberts, M.C., Rapoff, M. & Boyer, A. 2010, "The efficacy of adherence interventions for chronically ill children: a meta-analytic review", *Journal of Pediatric Psychology*, vol. 35, no. 4, pp. 368-382.
- Greenlaw, S.M., Yentzer, B.A., O'Neill, J.L., Balkrishnan, R. & Feldman, S.R. 2010, "Assessing adherence to dermatology treatments: a review of self-report and electronic measures", *Skin Research and Technology*, vol. 16, no. 2, pp. 253-258.
- Gross, R., Tierney, C., Andrade, A., Lalama, C., Rosenkranz, S., Eshleman, S.H., Flanigan, T., Santana, J., Salomon, N. & Reisler, R. 2009, "Modified directly observed antiretroviral therapy compared with self-administered therapy in treatment-naïve HIV-1-infected patients: a randomized trial", *Archives of Internal Medicine*, vol. 169, no. 13, pp. 1224.

- Grosset, K., Bone, I., Reid, J. & Grosset, D. 2006, "Measuring therapy adherence in Parkinson's disease: a comparison of methods", *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 77, no. 2, pp. 249-251.
- Grymonpre, R.E., Didur, C.D., Montgomery, P.R. & Sitar, D.S. 1998, "Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly", *The Annals of Pharmacotherapy*, vol. 32, no. 7/8, pp. 749-754.
- Gutierrez, J.P., Johns, B., Adam, T., Bertozzi, S.M., Edejer, T.T., Greener, R., Hankins, C. & Evans, D.B. 2004, "Achieving the WHO/UNAIDS antiretroviral treatment 3 by 5 goal: what will it cost?", *The Lancet*, vol. 364, no. 9428, pp. 63-64.
- Haberer, J.E., Kiwanuka, J., Nansera, D., Ragland, K., Mellins, C. & Bangsberg, D.R. 2012, "Multiple measures reveal antiretroviral adherence successes and challenges in HIV-infected Ugandan children", *PloS One*, vol. 7, no. 5, pp. e36737.
- Haberer, J.E., Cook, A., Walker, A.S., Ngambi, M., Ferrier, A., Mulenga, V., Kityo, C., Thomason, M., Kabamba, D., Chintu, C., Gibb, D.M. & Bangsberg, D.R. 2011, "Excellent Adherence to Antiretrovirals in HIV+ Zambian Children Is Compromised by Disrupted Routine, HIV Nondisclosure, and Paradoxical Income Effects", *PLoS ONE*, vol. 6, no. 4, pp. 1-8.
- Hansudewechakul, R., Jourdain, G. & Plangraun, N. 2006, "A comprehensive programme to strengthen adherence to antiretroviral drug therapy and achieve virological control in HIV infected children in Thailand", *Vulnerable Children & Youth Studies*, vol. 1, no. 2, pp. 180-191.
- Harrison, L., Ananworanich, J., Hamadache, D., Compagnucci, A., Penazzato, M., Bunupuradah, T., Mazza, A., Ramos, J.T., Flynn, J. & Rampon, O. 2013, "Adherence to Antiretroviral Therapy and Acceptability of Planned Treatment Interruptions in HIV-Infected Children", *AIDS and Behavior*, vol. 17, no. 1, pp. 193-202.
- Haynes, R.B., Ackloo, E., Sahota, N., McDonald, H.P. & Yao, X. 2008, "Interventions for enhancing medication adherence", *Cochrane Database Syst Rev*, vol. 2, no. 2.
- Hecht, F.M. 1998, "Measuring HIV treatment adherence in clinical practice", *AIDS Clinical Care*, vol. 10, no. 8, pp. 57-59.
- Heritier, S.R., Gebski, V.J. & Keech, A.C. 2003, "Inclusion of patients in clinical trial analysis: the intention-to-treat principle", *Medical Journal of Australia*, vol. 179, no. 8, pp. 438-440.
- Hien, H., Meda, N., Diagbouga, S., Zoure, E., Yaméogo, S., Tamboura, H., Somé, J., Ouiminga, A., Rouet, F. & Drabo, A. 2013, "24-Month adherence, tolerance and efficacy of once-a-day antiretroviral therapy with didanosine, lamivudine, and efavirenz in African HIV-1 infected children: ANRS 12103/12167", *African Health Sciences*, vol. 13, no. 2, pp. 287-294.
- Horne, R. 2006, "Compliance, Adherence, and Concordance Implications for Asthma Treatment", *CHEST Journal*, vol. 130, no. 1_suppl, pp. 65S-72S.

- Horne, R., Weinman, J., Barber, N., Elliott, R., Morgan, M. & Cribb, A. 2005, "Concordance, adherence and compliance in medicine taking", *London: NCCSDO*, , pp. 40-46.
- Horne, R. & Weinman, J. 1999, "Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness", *Journal of Psychosomatic Research*, vol. 47, no. 6, pp. 555-567.
- Horne, R., Weinman, J. & Hankins, M. 1999, "The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication", *Psychology and Health*, vol. 14, no. 1, pp. 1-24.
- Idigbe, E.O., Audu, R.A., Iroha, E.O., Akinsulie, A.O., Temiye, E.O., Ezeaka, V.C., Adetifa, I.M., Musa, A.Z., Onyewuche, J. & Ikundu, S.U. 2010, "T-lymphocyte subsets in apparently healthy Nigerian children", *International Journal of Pediatrics*, vol. 2010.
- Iroha, E., Esezobor, C.I., Ezeaka, C., Temiye, E.O. & Akinsulie, A. 2010, "Adherence to antiretroviral therapy among HIV-infected children attending a donor-funded clinic at a tertiary hospital in Nigeria", *African Journal of AIDS Research*, vol. 9, no. 1, pp. 25-30.
- Jaspan, H.B., Mueller, A.D., Myer, L., Bekker, L. & Orrell, C. 2011, "Effect of Caregivers' Depression and Alcohol Use on Child Antiretroviral Adherence in South Africa", *AIDS Patient Care & STDs*, vol. 25, no. 10, pp. 595-600.
- Jasti, S., Siega-Riz, A.M., Cogswell, M.E. & Hartzema, A.G. 2006, "Correction for errors in measuring adherence to prenatal multivitamin/mineral supplement use among low-income women", *The Journal of Nutrition*, vol. 136, no. 2, pp. 479-483.
- Johnson, S.S., Driskell, M., Johnson, J.L., Dymont, S.J., Prochaska, J.O., Prochaska, J.M. & Bourne, L. 2006a, "Transtheoretical model intervention for adherence to lipid-lowering drugs", *Disease Management*, vol. 9, no. 2, pp. 102-114.
- Johnson, M.O., Chesney, M.A., Goldstein, R.B., Remien, R.H., Catz, S., Gore-Felton, C., Charlebois, E. & Morin, S.F. 2006b, "Positive Provider Interactions, Adherence Self-Efficacy, and Adherence to Antiretroviral Medications Among HIV-Infected Adults: A Mediation Model", *AIDS Patient Care & STDs*, vol. 20, no. 4, pp. 258-268.
- Johnson, M.O., Neillands, T.B., Dilworth, S.E., Morin, S.F., Remien, R.H. & Chesney, M.A. 2007, "The Role of Self-Efficacy in HIV Treatment Adherence: Validation of the HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES)", *Journal of Behavioral Medicine*, vol. 30, no. 5, pp. 359-370.
- Johri, M. & Ako-Arrey, D. 2011, "The cost-effectiveness of preventing mother-to-child transmission of HIV in low-and middle-income countries: systematic review", *Cost Effectiveness and Resource Allocation*, vol. 9, no. 1, pp. 3.
- Kaai, S., Bullock, S., Sarna, A., Chersich, M., Luchters, S., Geibel, S., Munyao, P., Mandaliya, K., Temmerman, M. & Rutenberg, N. 2010, "Perceived stigma among patients receiving antiretroviral treatment: A prospective randomised trial comparing an m-DOT strategy with standard-of-care in Kenya", *SAHARA J (Journal of Social Aspects of HIV/AIDS Research Alliance)*, vol. 7, no. 2.

- Kahana, S.Y., Rohan, J., Allison, S., Frazier, T.W. & Drotar, D. 2013, "A meta-analysis of adherence to antiretroviral therapy and virologic responses in HIV-infected children, adolescents, and young adults", *AIDS and Behavior*, vol. 17, no. 1, pp. 41-60.
- Kalichman, S.C., Cain, D., Cherry, C., Kalichman, M. & Pope, H. 2005, "Pillboxes and antiretroviral adherence: prevalence of use, perceived benefits, and implications for electronic medication monitoring devices", *AIDS Patient Care & STDs*, vol. 19, no. 12, pp. 833-839.
- Kaplan, R.M., Bush, J.W. & Berry, C.C. 1976, "Health status: types of validity and the index of well-being.", *Health services research*, vol. 11, no. 4, pp. 478.
- Kardas, P., Lewek, P. & Matyjaszczyk, M. 2013, "Determinants of patient adherence: a review of systematic reviews", *Frontiers in pharmacology*, vol. 4, art. 91.
- Kelly, G.R., Mamon, J.A. & Scott, J.E. 1987, "Utility of the health belief model in examining medication compliance among psychiatric outpatients", *Social Science & Medicine*, vol. 25, no. 11, pp. 1205-1211.
- Kent, D.M., Mwamburi, D.M., Bennish, M.L., Kupelnick, B. & Ioannidis, J.P. 2004, "Clinical trials in Sub-Saharan Africa and established standards of care", *The Journal of the American Medical Association*, vol. 292, no. 2, pp. 237-242.
- Knobel, H., Alonso, J., Casado, J.L., Collazos, J., González, J., Ruiz, I., Kindelan, J.M., Carmona, A., Juega, J. & Ocampo, A. 2002, "Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study", *Aids*, vol. 16, no. 4, pp. 605-613.
- Kouanfack, C., Laurent, C., Peytavin, G., Ciaffi, L., Ngolle, M., Nkene, Y.M., Essomba, C., Calmy, A., Mpoudi-Ngolé, E. & Delaporte, E. 2008, "Adherence to antiretroviral therapy assessed by drug level monitoring and self-report in Cameroon", *Journal of Acquired Immune Deficiency Syndromes*, vol. 48, no. 2, pp. 216-219.
- Kripalani, S., Yao, X. & Haynes, R.B. 2007, "Interventions to enhance medication adherence in chronic medical conditions: a systematic review", *Archives of Internal Medicine*, vol. 167, no. 6, pp. 540.
- Kruse, R.L., Alper, B.S., Reust, C., Stevermer, J.J., Shannon, S. & Williams, R.H. 2002, "Intention-to-treat analysis: Who is in? Who is out?", *Journal of Family Practice*, vol. 51, no. 11, pp. 969-971.
- Landis, J.R. & Koch, G.G. 1977, "The measurement of observer agreement for categorical data", *Biometrics*, , pp. 159-174.
- Large, A. & Beheshti, J. 2001, "Focus Groups with Children: Do They Work?.", *Canadian Journal of Information and Library Science*, vol. 26, no. 2, pp. 77-89.
- le Roux, S., Cotton, M., Golub, J., le Roux, D., Workman, L. & Zar, H. 2009, "Adherence to isoniazid prophylaxis among HIV-infected children: a randomized controlled trial comparing two dosing schedules", *BMC medicine*, vol. 7, no. 1, pp. 67.

- Lederman, L.C. 1990, "Assessing educational effectiveness: The focus group interview as a technique for data collection 1", *Communication Education*, vol. 39, no. 2, pp. 117-127.
- Lennox, J.L., DeJesus, E., Lazzarin, A., Pollard, R.B., Madruga, J.V.R., Berger, D.S., Zhao, J., Xu, X., Williams-Diaz, A. & Rodgers, A.J. 2009, "Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial", *The Lancet*, vol. 374, no. 9692, pp. 796-806.
- LePrevost, M., Green, H., Flynn, J., Head, S., Clapson, M., Lyall, H., Novelli, V., Farrelly, L., Walker, A.S. & Burger, D.M. 2006, "Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children", *The Pediatric Infectious Disease Journal*, vol. 25, no. 6, pp. 533-537.
- Lesaffre, E. 2008, "Superiority, equivalence, and non-inferiority trials", *Bulletin of the NYU Hospital for Joint Diseases*, vol. 66, no. 2, pp. 150-154.
- Leventhal, H., Diefenbach, M. & Leventhal, E.A. 1992, "Illness cognition: using common sense to understand treatment adherence and affect cognition interactions", *Cognitive Therapy and Research*, vol. 16, no. 2, pp. 143-163.
- Levine, A.J., Hinkin, C.H., Marion, S., Keuning, A., Castellon, S.A., Lam, M.M., Robinet, M., Longshore, D., Newton, T. & Myers, H. 2006, "Adherence to antiretroviral medications in HIV: differences in data collected via self-report and electronic monitoring.", *Health Psychology*, vol. 25, no. 3, pp. 329.
- Liechty, C.A. & Bangsberg, D.R. 2003, "Doubts about DOT: antiretroviral therapy for resource-poor countries", *Aids*, vol. 17, no. 9, pp. 1383-1387.
- Likanonsakul, S., Wasi, C., Thepthai, C., Sutthent, R., Louisirirotchanakul, S., Chearskul, S., Vanprapa, N. & Lebnark, T. 1998, "The reference range of CD4 and CD8 T-lymphocytes in healthy non-infected infants born to HIV-1 seropositive mothers; a preliminary study at Siriraj Hospital.", vol. 29, no. 3.
- Liu, H., Miller, L.G., Hays, R.D., Golin, C.E., Zhao, H., Wenger, N.S. & Kaplan, A.H. 2006, "A comprehensive evaluation of survey questions for adherence to antiretroviral medications and exploratory analyses for identifying optimal sets of survey questions", *AIDS Patient Care & STDs*, vol. 20, no. 11, pp. 760-772.
- Lu, M., Safren, S.A., Skolnik, P.R., Rogers, W.H., Coady, W., Hardy, H. & Wilson, I.B. 2008, "Optimal recall period and response task for self-reported HIV medication adherence", *AIDS and Behavior*, vol. 12, no. 1, pp. 86-94.
- Luszczynska, A., Sarkar, Y. & Knoll, N. 2007, "Received social support, self-efficacy, and finding benefits in disease as predictors of physical functioning and adherence to antiretroviral therapy", *Patient Education and Counseling*, vol. 66, no. 1, pp. 37-42.
- Lyimo, R.A., van, d.B., Msoka, E., Hospers, H.J., van, d.V., Mushi, D. & de Bruin, M. 2011, "Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and

- acceptability of the Medication Event Monitoring System", *BMC Public Health*, vol. 11, no. 1, pp. 92-98.
- Lyon, M.E., Trexler, C., Akpan-Townsend, C., Pao, M., Selden, K., Fletcher, J., Addlestone, I.C. & D'Angelo, L.J. 2003, "A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project", *AIDS Patient Care and STDs*, vol. 17, no. 6, pp. 299-308.
- Majoko, F., Munjanja, S., Nyström, L., Mason, E. & Lindmark, G. 2007, "Randomised controlled trial of two antenatal care models in rural Zimbabwe", *BJOG: An International Journal of Obstetrics & Gynaecology*, vol. 114, no. 7, pp. 802-811.
- Mangoma, J., Chimbari, C. & Dhlomo, E. 2009, "An enumeration of orphans and analysis of the problems and wishes of orphans: the case of Kariba, Zimbabwe", *SAHARA J (Journal of Social Aspects of HIV/AIDS Research Alliance)*, vol. 5, no. 3, pp. 120-128.
- Mannheimer, S., Thackeray, L., Hullsiek, K.H., Chesney, M., Gardner, E.M., Wu, A.W., Telzak, E.E., Lawrence, J., Baxter, J. & Friedland, G. 2008, "A randomized comparison of two instruments for measuring self-reported antiretroviral adherence", *AIDS Care*, vol. 20, no. 2, pp. 161-169.
- Mannheimer, S.B., Morse, E., Matts, J.P., Andrews, L., Child, C., Schmetter, B. & Friedland, G.H. 2006, "Sustained Benefit from a Long-Term Antiretroviral Adherence Intervention: Results of a Large Randomized Clinical Trial", *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, pp. S41-S47.
- Marcellin, F., Spire, B., Carrieri, M.P. & Roux, P. 2013, "Assessing adherence to antiretroviral therapy in randomized HIV clinical trials: a review of currently used methods", *Expert Review of Anti-infective Therapy*, vol. 11, no. 3, pp. 239-250.
- Marhefka, S.L., Tepper, V.J., Brown, J.L. & Farley, J.J. 2006a, "Caregiver psychosocial characteristics and children's adherence to antiretroviral therapy", *AIDS Patient Care & STDs*, vol. 20, no. 6, pp. 429-437.
- Marhefka, S.L., Tepper, V.J., Farley, J.J., Sleasman, J.W. & Mellins, C.A. 2006b, "Brief Report: Assessing Adherence to Pediatric Antiretroviral Regimens Using the 24-Hour Recall Interview", *Journal of Pediatric Psychology*, vol. 31, no. 9, pp. 989-994.
- Martin, S., Elliott-DeSorbo, D.K., Wolters, P.L., Toledo-Tamula, M.A., Roby, G., Zeichner, S. & Wood, L.V. 2007, "Patient, caregiver and regimen characteristics associated with adherence to highly active antiretroviral therapy among HIV-infected children and adolescents", *The Pediatric Infectious Disease Journal*, vol. 26, no. 1, pp. 61-67.
- Martin, S., Elliott-DeSorbo, D., Calabrese, S., Wolters, P.L., Roby, G., Brennan, T. & Wood, L.V. 2009, "A Comparison of Adherence Assessment Methods Utilized in the United States: Perspectives of Researchers, HIV-Infected Children, and their Caregivers", *AIDS Patient Care & STDs*, vol. 23, no. 8, pp. 593-601.
- Mason, P.R. 2009, "Zimbabwe experiences the worst epidemic of cholera in Africa", *The Journal of Infection in Developing Countries*, vol. 3, no. 02, pp. 148-151.

- Mathews, W.C., Mar-Tang, M., Ballard, C., Colwell, B., Abulhosn, K., Noonan, C., Barber, R.E. & Wall, T.L. 2002, "Prevalence, predictors, and outcomes of early adherence after starting or changing antiretroviral therapy", *AIDS Patient Care and STDs*, vol. 16, no. 4, pp. 157-172.
- Mavhu, W., Berwick, J., Chirawu, P., Makamba, M., Copas, A., Dirawo, J., Willis, N., Araya, R., Abas, M.A., Corbett, E.L., Mungofa, S., Laver, S.M. & Cowan, F.M. 2013, "Enhancing Psychosocial Support for HIV Positive Adolescents in Harare, Zimbabwe", *PLoS ONE*, vol. 8, no. 7, pp. 1-10.
- Mc Van Rossum, A., Bergshoeff, A.S., LA Fraaij, P., Hugen, P.W., Hartwig, N.G., Geelen, S.P., Wolfs, T.F., Weemaes, C.M., De Groot, R. & Burger, D.M. 2002, "Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children", *The Pediatric Infectious Disease Journal*, vol. 21, no. 8, pp. 743-747.
- McCann, T.V., Clark, E. & Lu, S. 2008, "The self-efficacy model of medication adherence in chronic mental illness", *Journal of Clinical Nursing*, vol. 17, no. 11c, pp. 329-340.
- McDonnell, M., Turner, J. & Weaver, M.T. 2001, "Antecedents of adherence to antituberculosis therapy", *Public Health Nursing*, vol. 18, no. 6, pp. 392-400.
- McGrady, M.E. & Hommel, K.A. 2013, "Medication Adherence and Health Care Utilization in Pediatric Chronic Illness: A Systematic Review", *Pediatrics*, vol. 132, no. 4, pp. 730-740.
- McLafferty, I. 2004, "Focus group interviews as a data collecting strategy", *Journal of Advanced Nursing*, vol. 48, no. 2, pp. 187-194.
- Mellins, C.A., Brackis-Cott, E., Dolezal, C. & Abrams, E.J. 2004, "The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children", *The Pediatric Infectious Disease Journal*, vol. 23, no. 11, pp. 1035-1041.
- Mendelsohn, J.B., Schilperoord, M., Spiegel, P. & Ross, D.A. 2012, "Adherence to antiretroviral therapy and treatment outcomes among conflict-affected and forcibly displaced populations: a systematic review", *Conflict and Health*, vol. 6, no. 1, pp. 1-11.
- Menson, E.N., Walker, A.S., Sharland, M., Wells, C., Tudor-Williams, G., Riordan, F.A.I., Lyall, E. & Gibb, D.M. 2006, "Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study", *BMJ*, vol. 332, no. 7551, pp. 1183-1187.
- Mghamba, F.W., Minzi, O.M., Massawe, A. & Sasi, P. 2013, "Adherence to antiretroviral therapy among HIV infected children measured by caretaker report, medication return, and drug level in Dar Es Salaam, Tanzania", *BMC Pediatrics*, vol. 13, no. 1, pp. 95.
- Mhaskar, R., Alandikar, V., Emmanuel, P., Djulbegovic, B., Patel, S., Patel, A., Naik, E., Mohapatra, S. & Kumar, A. 2013, "Adherence to antiretroviral therapy in India: A

- systematic review and meta-analysis", *Indian Journal of Community Medicine*, vol. 38, no. 2, pp. 74-82.
- Miller, C. Center for International Health and Development, Boston University, 2007, "Children Affected by AIDS: A Review of the Literature on Orphaned and Vulnerable Children".
- Miller, L.G. & Chang, E.S. 2002, "Human immunodeficiency virus infection unresponsive to highly active antiretroviral therapy: Denial of poor medication adherence or recalcitrant infection?", *AIDS Patient Care and STDs*, vol. 16, no. 8, pp. 355-359.
- Mills, E.J., Nachega, J.B., Bangsberg, D.R., Singh, S., Rachlis, B., Wu, P., Wilson, K., Buchan, I., Gill, C.J. & Cooper, C. 2006, "Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators", *PLoS Medicine*, vol. 3, no. 11, pp. e438.
- Ministry of Health and Child Welfare, Zimbabwe 2010, *Guidelines for Antiretroviral Therapy in Zimbabwe*, National Drugs and Therapeutics Policy Advisory Committee, Harare.
- Ministry of Health and Child Welfare, Zimbabwe 2009a, *Report on the National HIV Drug Resistance Prevention and Assessment Strategy Zimbabwe, 2006-2008*, Zimbabwe Ministry of Health and Child Welfare, Harare.
- Ministry of Health and Child Welfare, Zimbabwe 2009b, *The Zimbabwe Program for the Prevention of Mother to child Transmission of HIV (PMTCT) Annual Report 2009*.
- Ministry of Health and Child Welfare, Zimbabwe 2008a, *Review of the National HIV and AIDS Treatment and Care Programme (OI/ART) 2004 – 2007*, Zimbabwe Ministry of Health and Child Welfare, Harare.
- Ministry of Health and Child Welfare, Zimbabwe 2008b, *The National OI/ART Programme 2008 Report*, Ministry of Health and Child welfare Zimbabwe, Harare.
- Ministry of Health and Child Welfare, Zimbabwe 2005, *Basic Approach to Starting ART in Children with HIV*, Zimbabwe Ministry of Health and Child Welfare, Harare.
- Ministry of Health and Child Welfare, Zimbabwe 2004, *HIV and AIDS Care. Plan for the Nationwide provision of Antiretroviral Therapy 2005-2007*, Zimbabwe Ministry of Health and Child Welfare, Harare.
- Minzi, O. & Naazneen, A. 2008, "Validation of self-report and hospital pill count using unannounced home pill count as methods for determination of adherence of antiretroviral therapy.", *Tanzania Journal of Health Research*, vol. 10, no. 2, pp. 84-88.
- Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P., Elbourne, D., Egger, M. & Altman, D.G. 2010, "CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials", *Bmj*, vol. 340.

- Moodley, D., Moodley, J., Coovadia, H., Gray, G., McIntyre, J., Hofmyer, J., Nikodem, C., Hall, D., Gigliotti, M. & Robinson, P. 2003, "A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1", *Journal of Infectious Diseases*, vol. 187, no. 5, pp. 725-735.
- Morgan, D.L. 1996, "Focus groups", *Annual Review of Sociology*, , pp. 129-152.
- Morisky, D.E., Ang, A., Krousel-Wood, M. & Ward, H.J. 2008, "Predictive validity of a medication adherence measure in an outpatient setting", *The Journal of Clinical Hypertension*, vol. 10, no. 5, pp. 348-354.
- Morisky, D.E., Green, L.W. & Levine, D.M. 1986, "Concurrent and predictive validity of a self-reported measure of medication adherence", *Medical Care*, vol. 24, no. 1, pp. 67-74.
- Morrison-Beedy, D., Côté-Arsenault, D. & Feinstein, N.F. 2001, "Maximizing results with focus groups: Moderator and analysis issues", *Applied Nursing Research*, vol. 14, no. 1, pp. 48-53.
- Mugore, L., Engelsmann, B., Ndoro, T., Dabis, F. & Perez, F. 2008, "An assessment of the understanding of the offer of routine HIV testing among pregnant women in rural Zimbabwe 1", *AIDS Care*, vol. 20, no. 6, pp. 660-666.
- Müller, A.D., Bode, S., Myer, L., Stahl, J. & von Steinbüchel, N. 2011, "Predictors of adherence to antiretroviral treatment and therapeutic success among children in South Africa", *AIDS Care*, vol. 23, no. 2, pp. 129-138.
- Müller, A.D., Bode, S., Myer, L., Roux, P. & von Steinbüchel, N. 2008, "Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa", *The Pediatric Infectious Disease Journal*, vol. 27, no. 3, pp. 257-262.
- Müller, A.D., Jaspan, H.B., Myer, L., Hunter, A.L., Harling, G., Bekker, L. & Orrell, C. 2011, "Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting", *AIDS and Behavior*, vol. 15, no. 2, pp. 422-431.
- Muñoz-Moreno, J.A., Fumaz, C.R., Ferrer, M.J., Tuldrà, A., Rovira, T., Viladrich, C., Bayés, R., Burger, D.M., Negredo, E. & Clotet, B. 2007, "Assessing self-reported adherence to HIV therapy by questionnaire: the SERAD (Self-Reported Adherence) Study", *AIDS Research and Human Retroviruses*, vol. 23, no. 10, pp. 1166-1175.
- Munro, S., Lewin, S., Swart, T. & Volmink, J. 2007, "A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS?", *BMC Public Health*, vol. 7, no. 1, pp. 104.
- Muyingo, S.K., Walker, A.S., Reid, A., Munderi, P., Gibb, D.M., Ssali, F., Levin, J., Katabira, E., Gilks, C. & Todd, J. 2008, "Patterns of individual and population-level adherence to antiretroviral therapy and risk factors for poor adherence in the first year of the DART trial in Uganda and Zimbabwe", *Journal of Acquired Immune Deficiency Syndromes*, vol. 48, no. 4, pp. 468-475.

- Nabukeera-Barungi, N., Kalyesubula, I., Kekitiinwa, A., Byakika-Tusiime, J. & Musoke, P. 2007, "Adherence to antiretroviral therapy in children attending Mulago Hospital, Kampala", *Annals of Tropical Paediatrics: International Child Health*, vol. 27, no. 2, pp. 123-131.
- Nachega, J.B., Chaisson, R.E., Goliath, R., Efron, A., Chaudhary, M.A., Ram, M., Morroni, C., Schoeman, H., Knowlton, A.R. & Maartens, G. 2010, "Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy", *AIDS*, vol. 24, no. 9, pp. 1273-1280.
- Nachega, J.B., Mills, E.J. & Schechter, M. 2010, "Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities", *Current Opinion in HIV and AIDS*, vol. 5, no. 1, pp. 70-77.
- Nachega, J.B., Uthman, O.A., Anderson, J., Peltzer, K., Wampold, S., Cotton, M.F., Mills, E.J., Ho, Y., Stringer, J.S. & McIntyre, J.A. 2012, "Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis", *AIDS*, vol. 26, no. 16, pp. 2039-2052.
- Naidoo, P., Taylor, M. & Jinabhai, C. 2010, "Adherence-monitoring practices by private healthcare sector doctors managing HIV and AIDS patients in the eThekweni metro of KwaZulu-Natal", *South African Family Practice*, vol. 52, no. 5, pp. 471-475.
- Newell, M., Coovadia, H., Cortina-Borja, M., Rollins, N., Gaillard, P. & Dabis, F. 2004, "Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis", *The Lancet*, vol. 364, no. 9441, pp. 1236-1243.
- NewsMedical.Net. 2007, 29 October 2007-last update, *Zimbabwe in line to reach antiretroviral treatment target, health official says*. [Homepage of NewsMedical.Net.], [Online]. Available: <<http://www.news-medical.net/?id=31861>>. [2008, September/9].
- Ngarina, M., Popenoe, R., Kilewo, C., Biberfeld, G. & Ekstrom, A.M. 2013, "Reasons for poor adherence to antiretroviral therapy postnatally in HIV-1 infected women treated for their own health: experiences from the Mitra Plus study in Tanzania", *BMC Public Health*, vol. 13, no. 1, pp. 1-9.
- Nicholson, O., Mellins, C., Dolezal, C., Brackis-Cott, E. & Abrams, E.J. 2006, "HIV treatment-related knowledge and self-efficacy among caregivers of HIV-infected children", *Patient Education and Counseling*, vol. 61, no. 3, pp. 405-410.
- Ogedegbe, G., Mancuso, C.A., Allegrante, J.P. & Charlson, M.E. 2003, "Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients", *Journal of Clinical Epidemiology*, vol. 56, no. 6, pp. 520-529.
- Ortego, C., Huedo-Medina, T.B., Llorca, J., Sevilla, L., Santos, P., Rodríguez, E., Warren, M.R. & Vejo, J. 2011, "Adherence to highly active antiretroviral therapy (HAART): a meta-analysis", *AIDS and Behavior*, vol. 15, no. 7, pp. 1381-1396.

- Oyugi, J.H., Byakika-Tusiime, J., Charlebois, E.D., Kityo, C., Mugerwa, R., Mugenyi, P. & Bangsberg, D.R. 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 Syndromes*, vol. 36, no. 5, pp. 1100-1102.
- Parikh, R., Mathai, A., Parikh, S., Shekhar, G.C. & Thomas, R. 2008, "Understanding and using sensitivity, specificity and predictive values", *Indian Journal of Ophthalmology*, vol. 56, no. 1, pp. 45-50.
- Parker, C.S., Price, M., Robert Gross MD, M., Metlay, J.P., Christie, J.D., Brensinger, C.M., MAR, C.W.N., Samaha, F.F. & Kimmel, S.E. 2007, "Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study", *Journal of General Internal Medicine*, vol. 22, no. 9, pp. 1254-1259.
- Partin, M.R., Grill, J., Noorbaloochi, S., Powell, A.A., Burgess, D.J., Vernon, S.W., Halek, K., Griffin, J.M., van Ryn, M. & Fisher, D.A. 2008, "Validation of self-reported colorectal cancer screening behavior from a mixed-mode survey of veterans", *Cancer Epidemiology Biomarkers & Prevention*, vol. 17, no. 4, pp. 768-776.
- Patel, S. & Dowse, R. 2013, "Understanding the medicines information-seeking behaviour and information needs of South African long-term patients with limited literacy skills", *Health Expectations*, in press.
- Paterson, D.L., Swindells, S., Mohr, J., Brester, M., Vergis, E.N., Squier, C., Wagener, M.M. & Singh, N. 2000, "Adherence to protease inhibitor therapy and outcomes in patients with HIV infection", *Annals of Internal Medicine*, vol. 133, no. 1, pp. 21-30.
- Pearson, C.R., Simoni, J.M., Hoff, P., Kurth, A.E. & Martin, D.P. 2007, "Assessing antiretroviral adherence via electronic drug monitoring and self-report: an examination of key methodological issues", *AIDS and Behavior*, vol. 11, no. 2, pp. 161-173.
- Perez, F., Engelsmann, B., Mushavi, A., Rusibamayila, A., Keatinge, J., Park, J., Maruva, M., Wood, R., Dabis, F. & Ciaranello, A.L. 2012, "Cost-Effectiveness of World Health Organization 2010 Guidelines for Prevention of Mother-to-Child HIV Transmission in Zimbabwe", .
- Petrie, A. 2009, *Medical statistics at a glance*, Wiley-Blackwell.
- Pham, P.A. 2009, "Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression", *AIDS Patient Care and STDs*, vol. 23, no. 10, pp. 803-807.
- Polisset, J., Ametonou, F., Arrive, E., Aho, A. & Perez, F. 2009, "Correlates of adherence to antiretroviral therapy in HIV-infected children in Lome, Togo, West Africa", *AIDS and Behavior*, vol. 13, no. 1, pp. 23-32.
- Pullar, T. 1991, "Compliance with drug therapy.", *British Journal of Clinical Pharmacology*, vol. 32, no. 5, pp. 535-539.

- Rabiee, F. 2004, "Focus-group interview and data analysis", *Proceedings of the Nutrition Society*, vol. 63, no. 4, pp. 655.
- Rasbach, D.A., Desruisseau, A.J., Kipp, A.M., Stinnette, S., Kheshti, A., Shepherd, B.E., Sterling, T.R., Hulan, T., McGowan, C.C. & Qian, H. 2013, "Active cocaine use is associated with lack of HIV-1 virologic suppression independent of nonadherence to antiretroviral therapy: Use of a rapid screening tool during routine clinic visits", *AIDS Care*, vol. 25, no. 1, pp. 109-117.
- Reddi, A., Leeper, S.C., Grobler, A.C., Geddes, R., France, K.H., Dorse, G.L., Vlok, W.J., Mntambo, M., Thomas, M. & Nixon, K. 2007, "Preliminary outcomes of a paediatric highly active antiretroviral therapy cohort from KwaZulu-Natal, South Africa", *BMC pediatrics*, vol. 7, no. 1, pp. 13.
- Reddington, C., Cohen, J., Baldillo, A., Toye, M., Smith, D., Kneut, C., Demaria, A., Bertolli, J. & Hsu, H. 2000, "Adherence to medication regimens among children with human immunodeficiency virus infection", *The Pediatric Infectious Disease Journal*, vol. 19, no. 12, pp. 1148-1153.
- Roberts, Gretchen M.Wheeler, J. GaryTucker, Nancy C.Hackler, ChrisYoung, KarenMaples,Holly D.Darville, Toni 2004, "Nonadherence With Pediatric Human Immunodeficiency Virus Therapy as Medical Neglect", *Pediatrics*, vol. 114, no. 3, pp. e346.
- Rogers, R.W. 1975, "A Protection Motivation Theory of Fear Appeals and Attitude Change1", *The Journal of Psychology*, vol. 91, no. 1, pp. 93-114.
- Rosenstock, I.M. 1966, "Why people use health services", *The Milbank Memorial Fund Quarterly*, vol. 44, no. 3, pp. 94-127.
- Royal Pharmaceutical Society of Great Britain & Marinker, M. 1997, *From compliance to concordance: achieving shared goals in medicine taking*, Royal Pharmaceutical Society, in partnership with Merck Sharp & Dohme.
- Russell, J., Krantz, S. & Neville, S. 2004, "The patient-provider relationship and adherence to highly active antiretroviral therapy", *Journal of the Association of Nurses in AIDS Care*, vol. 15, no. 5, pp. 40-47.
- Schneider, J., Kaplan, S.H., Greenfield, S., Li, W. & Wilson, I.B. 2004, "Better Physician-Patient Relationships Are Associated with Higher Reported Adherence to Antiretroviral Therapy in Patients with HIV Infection", *Journal of General Internal Medicine*, vol. 19, no. 11, pp. 1096-1103.
- Schulz, K.F., Altman, D.G. & Moher, D. 2010, "CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials", *BMC medicine*, vol. 8, no. 1, pp. 18.
- Seth, A., Gupta, R., Chandra, J., Maheshwari, A., Kumar, P. & Aneja, S. 2013, "Adherence to antiretroviral therapy and its determinants in children with HIV infection–Experience

- from Paediatric Centre of Excellence in HIV Care in North India", *AIDS Care*, , no. ahead-of-print, pp. 1-7.
- Shapiro, R.L., Thior, I., Gilbert, P.B., Lockman, S., Wester, C., Smeaton, L.M., Stevens, L., Heymann, S.J., Ndung'u, T. & Gaseitsiwe, S. 2006, "Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana", *AIDS*, vol. 20, no. 9, pp. 1281-1288.
- Shekelle, P., Maglione, M., Geetz, M.B., Wagner, G., Wang, Z., Hilton, L., Carter, J., Chen, S., Tringle, C., Mojica, W. & Newberry, S. 2007, "Antiretroviral (ARV) drug resistance in the developing world", *Evidence Report/Technology Assessment*, vol. (156), no. 156, pp. 1-74.
- Shi, L., Liu, J., Fonseca, V., Walker, P., Kalsekar, A. & Pawaskar, M. 2010a, "Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis", *Health and Quality of Life Outcomes*, vol. 8, no. 99, pp. 1-7.
- Shi, L., Liu, J., Koleva, Y., Fonseca, V., Kalsekar, A. & Pawaskar, M. 2010b, "Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices", *Pharmacoeconomics*, vol. 28, no. 12, pp. 1097-1107.
- Simoni, J.M., Frick, P.A. & Huang, B. 2006, "A longitudinal evaluation of a social support model of medication adherence among HIV-positive men and women on antiretroviral therapy.", *Health Psychology*, vol. 25, no. 1, pp. 74.
- Simoni, J.M., Frick, P.A., Lockhart, D. & Liebovitz, D. 2002, "Mediators of social support and antiretroviral adherence among an indigent population in New York City", *AIDS Patient Care and STDs*, vol. 16, no. 9, pp. 431-439.
- Simoni, J.M., Kurth, A.E., Pearson, C.R., Pantalone, D.W., Merrill, J.O. & Frick, P.A. 2006, "Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management", *AIDS and Behavior*, vol. 10, no. 3, pp. 227-245.
- Simoni, J.M., Montgomery, A., Martin, E., New, M., Demas, P.A. & Rana, S. 2007, "Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management", *Pediatrics*, vol. 119, no. 6, pp. e1371-e1383.
- Simoni, J.M., Pearson, C.R., Pantalone, D.W., Marks, G. & Crepaz, N. 2006, "Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load: a meta-analytic review of randomized controlled trials", *Journal of Acquired Immune Deficiency Syndromes*, vol. 43, pp. S23-S35.
- Skaik, Y.A.E. 2008, "Understanding and using sensitivity, specificity and predictive values", *Indian Journal of Ophthalmology*, vol. 56, no. 4, pp. 341.
- Skovdal, M., Campbell, C., Madanhire, C., Nyamukapa, C. & Gregson, S. 2011, "Challenges faced by elderly guardians in sustaining the adherence to antiretroviral therapy in HIV-infected children in Zimbabwe", *AIDS Care*, vol. 23, no. 8, pp. 957-964.

Southern African Development Community (SADC) 2007, *SADC Pharmaceutical Business Plan*, SDAC.

Steele, R.G. & Grauer, D. 2003, "Adherence to antiretroviral therapy for pediatric HIV infection: review of the literature and recommendations for research", *Clinical Child and Family Psychology Review*, vol. 6, no. 1, pp. 17-30.

Steele, R.G., Anderson, B., Rindel, B., Dreyer, M.L., Perrin, K., Christensen, R., Tyc, V. & Flynn, P.M. 2001, "Adherence to antiretroviral therapy among HIV-positive children: examination of the role of caregiver health beliefs", *AIDS Care*, vol. 13, no. 5, pp. 617-629.

Stolberg, H.O., Norman, G. & Trop, I. 2004, "Randomized controlled trials", *American Journal of Roentgenology*, vol. 183, no. 6, pp. 1539-1544.

Sutcliffe, C.G., van Dijk, J.H., Bolton, C., Persaud, D. & Moss, W.J. 2008, "Effectiveness of antiretroviral therapy among HIV-infected children in sub-Saharan Africa", *The Lancet Infectious Diseases*, vol. 8, no. 8, pp. 477-489.

Svarstad, B.L., Chewning, B.A., Sleath, B.L. & Claesson, C. 1999, "The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence", *Patient Education and Counseling*, vol. 37, no. 2, pp. 113-124.

Teri, L., McCurry, S.M., Logsdon, R.G., Gibbons, L.E., Buchner, D.M. & Larson, E.B. 2011, "A randomized controlled clinical trial of the Seattle protocol for activity in older adults", *Journal of the American Geriatrics Society*, vol. 59, no. 7, pp. 1188-1196.

Thior, I., Lockman, S., Smeaton, L.M., Shapiro, R.L., Wester, C., Heymann, S.J., Gilbert, P.B., Stevens, L., Peter, T. & Kim, S. 2006, "Breastfeeding Plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV Transmission in Botswana", *JAMA: the journal of the American Medical Association*, vol. 296, no. 7, pp. 794-805.

Thompson, K., Kulkarni, J. & Sergejew, A. 2000, "Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses", *Schizophrenia Research*, vol. 42, no. 3, pp. 241-247.

Tilson, H.H. 2004, "Adherence or compliance? Changes in terminology", *The Annals of Pharmacotherapy*, vol. 38, no. 1, pp. 161-162.

Townsend, C.L., Cortina-Borja, M., Peckham, C.S., de Ruiter, A., Lyall, H. & Tookey, P.A. 2008, "Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006", *AIDS*, vol. 22, no. 8, pp. 973-981.

Turissini, M.L., Nyandiko, W.M., Ayaya, S.O., Marete, I., Mwangi, A., Chemboi, V., Warui, L. & Vreeman, R.C. 2013, "The prevalence of disclosure of HIV status to HIV-infected children in Western Kenya", *Journal of the Pediatric Infectious Diseases Society*, vol. 2, no. 2, pp. 136-143.

- UNAIDS 2013a, *Global Report 2012: UNAIDS Report on the Global AIDS Epidemic*, ebookpartnership. com.
- UNAIDS 2013b, *Global Report: UNAIDS Report on the global AIDS Epidemic 2013*, UNAIDS.
- UNAIDS 2010, "UNAIDS 2010 Report on the Global AIDS Epidemic", .
- UNAIDS 2009, *AIDS epidemic update: December 2009*, WHO Regional Office Europe.
- UNAIDS 2007, *AIDS Epidemic Update: Special Report on HIV/AIDS: December 2007*.
- UNICEF 2009, "Children and AIDS. 4th Stocktaking Report 2009", New York: UNICEF, .
- Union, A. 2007, "Pharmaceutical manufacturing plan for Africa", *Third session of the African Union Conference of Ministers of Health, Johannesburg*.
- United Nations. Dept. of Public Information 2005, *The millennium development goals: report 2005*, United Nations Publications.
- Van Boven, J.F., Chavannes, N.H., van der Molen, T., Rutten-van Mölken, M.P., Postma, M.J. & Vegter, S. 2013, "Clinical And Economic Impact Of Non-Adherence In Copd: A Systematic Review", *Respiratory Medicine*, vol. 108, no. 1, pp. 103-113.
- Van der Plas, A., Scherpbier, H., Kuijpers, T. & Pajkrt, D. 2013, "The effect of different intervention programs on treatment adherence of HIV-infected children, a retrospective study", *AIDS Care*, vol. 25, no. 6, pp. 738-743.
- Van Dyke, R.B., Lee, S., Johnson, G.M., Wiznia, A., Mohan, K., Stanley, K., Morse, E.V., Krogstad, P.A. & Nachman, S. 2002, "Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection", *Pediatrics*, vol. 109, no. 4, pp. e61-e61.
- Van Griensven, J., De Naeyer, L., Uwera, J., Asiimwe, A., Gazille, C. & Reid, T. 2008, "Success with antiretroviral treatment for children in Kigali, Rwanda: experience with health center/nurse-based care", *BMC Pediatrics*, vol. 8, no. 1, pp. 39.
- Veenstra, N., Whiteside, A., Gibbs, A. & Lalloo, D. 2010, "Unplanned ART treatment interruptions in southern Africa: what can we do to minimise the long-term risks", *KwaZulu-Natal, South Africa: Health Economics and HIV/AIDS Research Division (HEARD)*.
- Velligan, D., Wang, M., Diamond, P., Glahn, D., Castillo, D., Bendle, S., Lam, Y.F., Ereshefsky, L. & Miller, A. 2007, "Relationships among subjective and objective measures of adherence to oral antipsychotic medications", *Psychiatric Services*, vol. 58, no. 9, pp. 1187-1192.

- Ventura-Cerdá, J., Mínguez-Gallego, C., Fernández-Villalba, E., Alós-Almiñana, M. & Andrés-Soler, J. 2005, "[Simplified scale for medication adherence related problems in anti-retroviral therapy]", *Farmacia Hospitalaria: Organo Oficial de Expresion Cientifica de la Sociedad Espanola de Farmacia Hospitalaria*, vol. 30, no. 3, pp. 171-176.
- Vermeire, E., Hearnshaw, H., Van Royen, P. & Denekens, J. 2001, "Patient adherence to treatment: three decades of research. A comprehensive review", *Journal of Clinical Pharmacy and Therapeutics*, vol. 26, no. 5, pp. 331-342.
- Viera, A.J. & Garrett, J.M. 2005, "Understanding interobserver agreement: the kappa statistic", *Family Medicine*, vol. 37, no. 5, pp. 360-363.
- Vik, S.A., Maxwell, C.J. & Hogan, D.B. 2004, "Measurement, correlates, and health outcomes of medication adherence among seniors", *The Annals of Pharmacotherapy*, vol. 38, no. 2, pp. 303-312.
- Vitolins, M.Z., Rand, C.S., Rapp, S.R., Ribisl, P.M. & Sevick, M.A. 2000, "Measuring adherence to behavioral and medical interventions", *Controlled Clinical Trials*, vol. 21, no. 5, pp. S188-S194.
- Vreeman, R.C., Nyandiko, W.M., Sang, E., Musick, B.S., Braitstein, P. & Wiehe, S.E. 2009, "Impact of the Kenya post-election crisis on clinic attendance and medication adherence for HIV-infected children in western Kenya", *Conflict and Health*, vol. 3, no. 5.
- Vreeman, R.C., Wiehe, S.E., Ayaya, S.O., Musick, B.S. & Nyandiko, W.M. 2008a, "Association of antiretroviral and clinic adherence with orphan status among HIV-infected children in Western Kenya", *Journal of Acquired Immune Deficiency Syndromes*, vol. 49, no. 2, pp. 163-170.
- Vreeman, R.C., Wiehe, S.E., Pearce, E.C. & Nyandiko, W.M. 2008b, "A systematic review of pediatric adherence to antiretroviral therapy in low-and middle-income countries", *The Pediatric Infectious Disease Journal*, vol. 27, no. 8, pp. 686-691.
- Vreeman, R.C., Nyandiko, W.M., Ayaya, S.O., Walumbe, E.G., Marrero, D.G. & Inui, T.S. 2010, "The Perceived Impact of Disclosure of Pediatric HIV Status on Pediatric Antiretroviral Therapy Adherence, Child Well-Being, and Social Relationships in a Resource-Limited Setting", *AIDS Patient Care & STDs*, vol. 24, no. 10, pp. 639-649.
- Vriesendorp, R., Cohen, A., Kristanto, P., Vrijens, B., Rakesh, P., Anand, B., Iwebor, H.U. & Stiekema, J. 2007, "Adherence to HAART therapy measured by electronic monitoring in newly diagnosed HIV patients in Botswana", *European Journal of Clinical Pharmacology*, vol. 63, no. 12, pp. 1115-1121.
- Wachholz, N.I.R. & Ferreira, J. 2007, "Adherence to antiretroviral therapy in children: a study of prevalence and associated factors", *Cadernos de Saúde Pública*, vol. 23, pp. S424-S434.

- Wahl, C., Gregoire, J., Teo, K., Beaulieu, M., Labelle, S., Leduc, B., Cochrane, B., Lapointe, L. & Montague, T. 2005, "Concordance, compliance and adherence in healthcare: closing gaps and improving outcomes", *Healthcare Quarterly*, vol. 8, no. 1, pp. 65-70.
- Walker, S.A., Prendergast, A.J., Mugenyi, P., Munderi, P., Hakim, J., Kekitiinwa, A., Katabira, E., Gilks, C.F., Kityo, C., Nahirya-Ntege, P., Nathoo, K., Gibb, D.M. 2012, "Mortality in the Year Following Antiretroviral Therapy Initiation in HIV-Infected Adults and Children in Uganda and Zimbabwe.", *Clinical Infectious Diseases*, vol. 55, no. 12, pp. 1707-1718.
- Wang, H., He, G., Li, X., Yang, A., Chen, X., Fennie, K.P. & Williams, A.B. 2008, "Self-Reported Adherence to Antiretroviral Treatment among HIV-Infected People in Central China", *AIDS Patient Care & STDs*, vol. 22, no. 1, pp. 71-80.
- Ware, N.C., Idoko, J., Kaaya, S., Biraro, I.A., Wyatt, M.A., Agbaji, O., Chalamilla, G. & Bangsberg, D.R. 2009, "Explaining adherence success in sub-Saharan Africa: an ethnographic study", *PLoS medicine*, vol. 6, no. 1, pp. e1000011.
- Warner, L.M., Schüz, B., Aiken, L., Ziegelmann, J.P., Wurm, S., Tesch-Römer, C. & Schwarzer, R. 2013, "Interactive effects of social support and social conflict on medication adherence in multimorbid older adults", *Social Science & Medicine*, vol. 87, pp. 23-30.
- Weigel, R., Makwiza, I., Nyirenda, J., Chiunguzeni, D., Phiri, S. & Theobald, S. 2009, "Supporting children to adhere to anti-retroviral therapy in urban Malawi: multi method insights", *BMC Pediatrics*, vol. 9, no. 1, pp. 45.
- Welsh, E., Gettinby, G. & Nolan, A. 1993, "Comparison of a visual analogue scale and a numerical rating scale for assessment of lameness, using sheep as a model.", *American Journal of Veterinary Research*, vol. 54, no. 6, pp. 976-983.
- Wendel, C.S., Mohler, M.J., Kroesen, K., Ampel, N.M., Gifford, A.L. & Coons, S.J. 2001, "Barriers to use of electronic adherence monitoring in an HIV clinic", *The Annals of Pharmacotherapy*, vol. 35, no. 9, pp. 1010-1015.
- Wiener, L., Riekert, K., Ryder, C. & Wood, L.V. 2004, "Assessing medication adherence in adolescents with HIV when electronic monitoring is not feasible", *AIDS Patient Care & Stds*, vol. 18, no. 9, pp. 527-538.
- Williams, P.L., Storm, D., Montepiedra, G., Nichols, S., Kammerer, B., Sirois, P.A., Farley, J. & Malee, K. 2006, "Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection", *Pediatrics*, vol. 118, no. 6, pp. e1745-e1757.
- Wittes, J. 2002, "Sample size calculations for randomized controlled trials", *Epidemiologic Reviews*, vol. 24, no. 1, pp. 39-53.
- Wolf, M.S., Davis, T.C., Osborn, C.Y., Skripkauskas, S., Bennett, C.L. & Makoul, G. 2007, "Literacy, self-efficacy, and HIV medication adherence", *Patient Education and Counseling*, vol. 65, no. 2, pp. 253-260.

World Health Organisation 2003, "Adherence to long-term therapies: evidence for action".

World Health Organisation 2012, *Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants*.

World Health Organization 2013, "Consolidated guidelines on general HIV care and the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach".

World Health Organization 2010a, "Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infections in Infants: Recommendations for a public health approach–2010 version".

World Health Organization 2010b, "Antiretroviral therapy for HIV infection in infants and children: Recommendations for a public health approach (2010 revision)", *Geneva, WHO*.

World Health Organization 2010c, "MDG 6: combat HIV/AIDS, malaria and other diseases", *Geneva: WHO*.

World Health Organization 2006a, *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access: recommendations for a public health approach*, World Health Organization, Department of HIV/AIDS.

World Health Organization 2006b, *Antiretroviral Therapy of HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a Public Health Approach*, World Health Organization.

World Health Organization 2006c, *Antiretroviral Therapy of HIV Infection in Infants and Children: Towards Universal Access: Recommendations for a Public Health Approach*, World Health Organization.

World Health Organization & UNAIDS, U. 2011, "Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011", *Geneva: World Health Organization*.

Zimbabwe 2010, *United Nations General Assembly Special Session Report on HIV and AIDS: Follow-up to the Declaration of Commitment on HIV and AIDS: Zimbabwe Country Report 2008-2009*, Government of Zimbabwe.

APPENDICES

Appendix 1

Group 1: Modified PACTG Self-Reported Adherence Tool

“Most people with HIV have many different medicines to take at different times during the day. Many people find it hard to always remember to take [to give] their medicines. They get busy and forget to carry their medicines with them, or they get confused about the instructions and decide not to take [to give] them. Some people just decide it would be nice to have a day off. We need to understand how children with HIV and their caregivers are really doing with the child’s medication taking. Please tell us what you are actually doing. Don’t worry about telling us that the child was not taking all the medicines. We need to know what is really happening, not what you think we want to hear.”

Establishing the actual tablets the child is taking and complete the table below up to column D.

Names of individual drugs in regimen	Name of tablets (FDC or not)	Dose (number of tablets)	Number of doses per day	Doses Missed					
				Day(s) ago			Past days		
				1	2	3	7	14	30
A	B	C	D	E	F	G	H	I	J

Show the caregiver the tablets that the child is taking (from the samples that you have) and proceed as follows:

“These are the tablets your child was taking in the past month”,

“Now for this (drug name) (*show picture of tablet/medicine*), it looks like this medicine needs to be taken _____ times each day.” (*Refer to the prescribed number of times, not the number reported by the subject.*)

“Now think about yesterday. Of the prescribed doses, how many did the child miss?

Record this number in column E.

“Now think about the day before that. That would have been _____ Of the prescribed doses, how many did the child miss?

Record this number in column F.

“Go back just one more day. That would have been _____. Remember some of the things that happened 3 days ago. Of the prescribed doses, how many did the child miss?

Record this number in column G.

“Now think about the past seven days since _____ (same day in the past week) last week. Of the prescribed doses, how many did the child miss?

Record this number in column H

Think about the past two weeks since _____ (same day two weeks ago) last week but one. Of the prescribed doses, how many did the child miss?

Record this number in column I

Finally on this medicine, think about the past 30 days,. Of the prescribed doses, how many did the child miss?

Record this number in column J

Repeat for each ARV medicine the child is taking until they are finished.

Appendix 2
The Adapted Morisky 8-Item Scale

*I will now ask you some questions about the child's medication taking.
Ndichakubvunzai mibvunzo pamusoro pekumwira kwemushonga nemwana.*

Item	Response/ score		Score
	Yes	No	
Does the child sometimes miss taking his/her medicine? Mwana anomborega kumwa mishonga yake apo anonga achifanira kumwa here.	0	1	
People sometimes miss taking their medicines for reasons other than forgetting. Thinking over the past two weeks, were there any days when the child did not take his/her medicine? Dzimwe nguva zvinoitika kuti vanhu vanomborega kumwa mishonga yavo sezvavanofanira kuita nekuda kwezvimwe zvikonzero zviri kunze kwekukanganwa. Muchifunga nezvemasvondo maviri akapfuura, pane here mwame mazuva ayo mwana asina kumwa mishonga yake?	0	1	
Has the child ever reduced or stopped taking his/her medicine without telling the doctor for any reason? Mwana ane apo akamborega kumwa kana kuderedza uvandu hwemishonga yaanomwa here kana kutorega kumwa mishonga yake asina kutaurira chiremba?	0	1	
When the child travels or is not at home for other reasons does he sometimes fail to take the medicine with him/her? Apo mwana anofamba rwendo kana kuti asiri pamba nekuda kwezvimwe zvikonzero, anomborega kutakura mishonga yake pakufamba uku here?	0	1	
Did the child take all his/her medicine yesterday? Mwana akamwa mishonga yake yese here nezuro?	1	0	
When the child feels better, does s/he sometimes stop taking his/her medicine? Apo mwana anonzwa zvirinani, anomborega kumwa mishonga yake here?	0	1	
Giving the child medication every day is a real inconvenience for some people, Do you ever feel hassled about sticking to the child's treatment plan? Chinhu chinopingaidza chose kuti upe mwana mishonga mazuva ose. Munomboona sokuti chinhu chinokunetsai here kuti mupe mwana mishonga yake	0	1	

muchitevedzera mamwiro aanofanira kuita chaiwo.			
How often do you have difficulty remembering to give your child medicine (encircle) Kangani apo munova nedambudziko kuti mutondere kupa mwana mishonga yake.	0	1	
1. Never /rarely (Kana/nenguva irikurekure) 2. Once in a while (nenguva iri kure) 3. Sometimes (dzimwe nguva) 4. Usually (Nguva dzakawanda) 5. All the time (nguva dzose)	2,3,4,or 5	1	
Total Score (range 0-8)			

Appendix 3

Group 2: New Adherence Monitoring Tool for Children on ART: past 10 days, visually and verbally cued self-report tool.

Some people have difficulties in giving their child medication daily on time. This may be as a result of getting too busy, simply forgetting, and the child being away from home or some unusual situation that may arise and disturb the routine of life. We would like to know and understand how you and the child are doing regarding the child's medication taking. *Vamwe vanhu vanova nedambudziko pakupa mwana wavo mishonga yake mazuva ose panguva dzakafanira. Izvi zvinogona kubudikidza nekubatikana, nekukanganwa, nekuti mwana afamba kubvapamusha, kana kuti mhingaidzo dzinovanika pakurarama. Tingada kuziva nokunzwisisa kuti imi nemwana murikuita zvakadini pamusoro pekumwiwa kwemishonga nemwana.*

Please tell us what is actually happening on the child's medication taking. This will help us to understand more about the child's treatment. Telling us the truth about how the child is taking his/her medication, even when he has missed his medication many times, will help (us) in giving the child the best help possible on his treatment. Your child's treatment will not be compromised even when you report that the child missed some doses. *Tinokumbirisa kuti mutiudze zvirikuitika chaizvo pamusoro pemamwiro arikuita mwana mishonga yake. Izvi zvinovedzera kunzwisisa kwedu pamusoro pemapirwo emwana. Kutiudza chokwadi pamusoro pekumwa kurikuita mwana mishonga yake, kunyangwe kutiudza chokwadi apo asina kumwa mishonga, kunotibatsira pakuti mwana avane rubatsiro rwepamusorosoro runokwanisika pakurapwa kwake. Kunyange mukatiudza kuti mwana akamborega kumwa mishonga yake paneimwe nguwa iyo aifanira kumwa, izvi hazvizokangaidzi marapirwo emwana uyu.*

Can you identify the pills the child is taking on the pictures below, Please point to the medicine that the child is taking? *Munogona here kupatsanura mishonga irikumwiwa pamifananidzo yemapiritsi iripasi. Tinokumbira kuti mutinon zere mishonga iyo mwana arikumwa pamifananidzo iripazasi.*



1. Can identify all
any

2. Can identify part

3. Cannot identify

How many times a day should the child take each of these medicines? *Mwana anofanira kumwa umwe neumwe wemishanga yake kangani pazuva?*

Correct 1. Yes 2. No

How many pills from each of his/her medication should the child take each time i.e morning, noon and evening? *Mwana anofanira kumwa mapiritsi mangani emushonga umwe neumwe vaari kumwa mangwanani, masikati nemanheru.*

Correct 1. Yes 2. No

Can you try and remember what you were doing on Sunday this week? (You can tell me if this is alright for you.) *Mungatondera here kuti musi we Svondo yesvondo rino maibatei? (Munogona kundiudza kana makasununguka nazvo.)*

In the table below, each circle stands for one tablet. Starting with the weekend (Sartuday), can you shade on the number of circles that are equivalent to the number of tablets that the child missed out each day of this week, morning and evening until today,.....(day). Please note that we are talking about the antiretroviral drugs only (excluding cotrimoxazole)

Mumufananidzo unotewera, kadenderedzwa kogakoga kanomirira piritsi rimwe. Muchitanga ne mugovera uchangodarika, mungadzurudzuta here nechinyoreso ichi madenderedzwa aneuwandu hwemapiritsi ayo mwana akaregera kumwa as iye aifanira kunge aamwa pazuva rogaroga, mangwanani masikati kana manheru kusvika nhasi (musaverenga mapiritsi ema Cotri)

Day (Zuva revhiki)	Morning dose (Mapiritsi anomwiwa mangwanani) 	Evening dose (Mapiritsi anomwiwa manheru) 	Interviewer comment
Saturday Mugovera			
Sunday (this week) Svondo			
Monday Muvhuro			
Tuesday Chipiri			
Wednesday Chitatu			
Thursday China			
Friday Chishanu			

Can you try and remember what you were doing on Sunday last week. In the table below, each circle stands for one tablet. Starting with the weekend (Saturday, *but including the preceding Friday if the interview date is a Monday*), can you shade on those circles that stand for the tablets that the child missed out each day of last week, morning and evening until Friday last week (of the same week).

Mungatondera here kuti musi we Svondo yesvondo rapera maibatei. (Munogona kundiudza kana makasununguka nazvo.)

Mumufananidzo unotewera, kadenderedzwa kogakoga kanomirira piritsi rimwe. Muchitanga ne mugovera wevhiki yapfuura pamberi (mungangotanga pachishanu chacho kana musi vamurikubvunzwa nezvegwaro rino uri muvhuro), mungadzurudzuta here nechinyoreso ichi madenderedzwa aneuwandu hwemapiritsi ayo mwana akaregera kumwa as iye aifanira kunge akaamwa pazuva rogaroga, mangwanani masikati kana manheru musvondo rapera kusvika chishanu chevhiki rapera. (musaverenga mapiritsi ema Cotri)

Day	Morning dose 	Evening dose 	Interviewer comment
Friday (last week but one)			
Saturday			
Sunday (last week)			
Monday			

Tuesday			
Wednesday			
Thursday			
Friday (last week)			

Appendix 4

Pill-counts adherence form

Clinic-based pill counts/medicine measurement

Were the remaining pills, if any, brought to the health facility?

1. Yes there are some remaining pills
2. No there were no remaining pills. Pills were finished on.....(day and month)
3. No, pills were left at home (Do not administer this tool)

Drug name (single drug or FDC)	Number of tablets/ ml. per dose	Doses per day	Date of last refill (dd/mm)	Quantity dispensed at last refill	Residual quantity at last refill (self-reports)	Quantity returned at current visit

Starting time.....

Finishing time.....

Appendix 5

Questionnaire

Study on Adherence to Antiretroviral Therapy in Children in Zimbabwe

SECTION A: IDENTIFICATION INFORMATION

1. Identification information

1.1. Site number (*encircle*) 1=Urban Central Hospital 2=District Rural Hospital

1.2. Study-specific ID Number for child (as allocated on recruitment from list of study participants)
|_|_|_|_|

1.3. Date |_|_|_|_| dd/mm/yy 1.4. Initials of interviewer |_|_|

2. Verify eligibility of potential respondent

(Respondent should be the current primary care giver or secondary caregiver who stayed with the child in the same household in the past 30 days)

2.1. Are you the first adult who is primarily responsible for this child's medication-taking?
1. Yes 2. No

OR

2.2. Are you also responsible for the child's medication-taking as a secondary person to the primary caregiver?
1. Yes 2. No

AND

2.3. Have you been staying with the child in the same household since the.....?(provide a date that is 30days prior to the interview date)
1. Yes 2. No

2.4. Eligible (yes to both 2.1 and 2.3 OR yes to both 2.2 and 2.3)?

1. Yes (*proceed*)
2. No (*stop interviews*)

Who responded to the question?

1. Primary caregiver
2. Secondary caregiver

2.5. Randomisation group: Group 1= Control Group 2= Intervention

SECTION B: ADHERENCE ASSESSMENT AND KNOWLEDGE ON TREATMENT REGIMEN

3. Caregiver's knowledge of child's treatment regimen

Assess knowledge of antiretroviral medication.. Write names of all drugs mentioned including those which are not ARVs

I am going to briefly ask you about your experiences caring for the child and giving medication to the child

Can you tell me the names of the medicines your child is taking? (Ndichakubvunzai pamusoro pemachengetero amurikuita mwana nekumupa kwamurikuita mapiritsi ake. Mungandiudzawo here mazita emapiritsi ayo mwana arikumwa parizvino)

1. 5.
2. 6.
3. 7.
4. 8.

Assess knowledge on ARVs only and encircle the appropriate responses in the questions below

Knowledge of regimen	Yes	No	Score if yes	Actual score
Can you tell me the names of the HIV medicine the child is taking even if they are combined in one tablet (Mungandiudza mazita emishonga iyo mwana arikumwa here kunyange mupiritsi rimwe makasanganiswa mishonga miiri.)				
3.1. Knows the three drugs the child is taking by individual name (mentioning the names of the individual drugs that are in fixed dose combination (FDC) form) (one point for each name)	1-2-3	0	1-3	
3.2. Knows the name(s) of the FDC (s)	1	-1 (0 if N/A)	1	
Knowledge of dosages				
Can you tell me how the child takes his/her medication?				
3.3. Knows the doses for all ARVs	1	0	1	
3.4. Knows the frequency for all ARVs	1	0	1	
3.5. Knows the time intervals for all ARV drugs	1	0	1	
ART-related knowledge	Response (score)	Response (score)	Response (score)	
3.6. When one is on ARVs the CD4 count is expected to go up, down or not sure? (Kana munhu achimwa mapiritsi emaARVs Masoja anorwisa zvirwere mumuviri wake anonzi maCD4 anotarisirwa kuwedzera here kana kuti kuderera?) (Explain-----to remove the role of chance)	Up (1)	Down (0)	Not sure (0)	
3.7. When one is on ARVs the viral load is expected to go up or down or not sure? (Kana munhu achimwa mapiritsi emaARVs utachiwana hweHIV hurimumuviri wake hunotarisirwa kuwedzera here kana kuderera ?) (Explain---to remove the role of chance)	Up (0)	Down (1)	Not sure (0)	
3.8. If a person on ARVs does not take his medication as required, the virus may become resistant (Ichokwadi here kana kuti manyepo kuti kana munhu arikumwa mapiritsi ema ARVs akasanyatsomwa mapiritsi aya sezvinotarisirwa, utachiwana hurimumuviri make hunogona kusazorapika zvakare kunyangwe akazotanga kunyatsomwa mapiritsi aya zvakanaka)	True (1)	False (0)	Not sure (0)	
Total score(range: -1 to 10)				

4. Adherence Monitoring (administer tool to parent at this point and **Not** child)

Group 1: Control Group

Apply the following adherence monitoring tools in the same order: 1. Self-Report Tool, 2. The Morisky 8-Item Medication Adherence Scale and 3. Returned Pill Count tool, to assess adherence among children in the control group.

Group 2-Intervention group

Apply the following adherence monitoring tools in the same order: 1. Newly -developed tool, 2. the Morisky 8-item Medication Adherence Scale 3. Returned Pill Count tool, to assess adherence among children in the intervention group

SECTION C: SOCIO-DEMOGRAPHIC INFORMATION OF CAREGIVER AND CHILD

5. Socio-demographic information of primary caregiver and secondary caregiver

The following questions relate to the person who is primarily(most) responsible for the child's medication taking and daily welfare i.e. primary caregiver (the secondary caregiver respondent should provide this information regarding the primary caregiver, if not sure put code 99)

- 5.1. What is the relationship of the primary caregiver to the child? (**Munhu anova aripanyanga panyaya dzekuchengeta mwana uyu aneukama hwakadii nemwana uyu?**)

1. Biological mother	Go to Q 5.3
2. Biological father	
3. Brother	
4. Sister	
5. Grandmother	Proceed to next Q 5.2
6. Grandfather	
7. Stepmother	
8. Uncle	
9. Aunt	
10. Other, specify.....	

- 5.2. **If** primary caregiver is not mother, father, brother or sister, specify whether the relationship is maternal or paternal

(Ukama uhu ndehwekwamai here kana kuti kwababa?)

1. Maternal
2. Paternal

- 5.3. **If** primary caregiver **is not the mother**, why is the mother not available to care for the child? (**Sei mai wemwana uyu va siri ivo vanomuchengeta**)

1. Passed away
2. Divorced
3. Abandoned the child
4. Working in another location
5. Others (Specify).....
99. Not sure

- 5.4. Age of primary caregiver.....years (**Muchengeti uyu anemakore mangani ekuberekwa**)
99. Not sure

- 5.5. Sex of primary caregiver. **Munhu rume here kana munhukadzi?**
1. Male
 2. Female
- 5.6. Marital status of primary caregiver (**Muchengeti uyu akamirasei panyaya dzekuroora kana kuroorwa, kana akaroorwa kana kuroora, paguru here kana kuti kwete?**)
1. Never married
 2. Married monogamous
 3. Married polygamous
 4. Divorced or separated
 5. Widowed
 6. Prolonged conjugal separation
 7. Others (specify).....
- 5.7. Level of education of primary caregiver (**Muchengeti uyu akadzidza kusvika gwaro ripi?**)
1. None
 2. Primary
 3. Form 1 and 2
 4. Form 3 and 4
 5. Form 5 and 6
 99. Not sure
- 5.8. Tertiary level qualifications of primary caregiver (specify the training) (**Ane basa raakadzidzira here? Nderipi?**)
1. None
 2. Non-formal training.....
 3. Certificate.....
 4. Diploma.....
 5. Degree.....
 99. Not sure
- 5.9. Religious affiliation of primary caregiver (tick only one most applicable) (**Anopinda chitendero chipi?**)
1. Apostolic (specify which one).....
 2. Catholic
 3. Protestant (specify which one).....
 4. Pentecostal (specify which one).....
 5. Atheist
 6. Traditional
 7. Moslem
 8. Others (specify).....
 99. Not sure
- 5.10. Nationality of primary caregiver. (**Chizvarwa chenyika ipi?**)
1. Zimbabwean
 2. Malawian
 3. Others (specify).....
 99. Not sure

5.11. How does the primary caregiver spend most of his/her days? (**Muchengeti vemwana uyu anovanzobatei mazuva mazhinji ekurarama kwake?**)

1. At home doing normal home chores
2. At home self employed
3. Away from home self employed
4. Away from home fully employed
5. Away from home partly employed
6. Others (specify).....
99. Not sure

5.12. For how long has the primary caregiver lived with the child?.....Years and months (**Agara nemwana uyu nguva yakareba zvakadii?**)

99. Not sure

Demographic information of secondary caregiver (if primary caregiver is the respondent, s/he should provide information on the secondary caregiver, If secondary caregiver is respondent, s/he should provide information about himself or herself.)

Does the child have a secondary caregiver 1. Yes 2. No,(if yes proceed with this section, if no skip this section.)

5.13. What is the relationship of the secondary caregiver to the child? (**muneukama hwakadii nemwana uyu?**)

11. Biological mother
12. Biological father
13. Brother
14. Sister
15. Grandmother
16. Grandfather
17. Stepmother
18. Uncle
19. Aunt
20. Other, specify.....

5.14. Age of secondary caregiver.....years (**Mune makore mangani ekuzvarwa?**)

99. Not sure

5.15. Sex of secondary caregiver

1. Male
2. Female

5.16. Level of education of secondary caregiver (**Makadzidza kusvika mugwaro ripi?**)

1. None
2. Primary
3. Form 1 and 2
4. Form 3 and 4
5. Form 5 and 6

5.17. Tertiary level qualifications of secondary caregiver (specify the training) **(Munebasa ramakadzidzira here? Nderipi?)**

1. None
2. Non-formal training.....
3. Certificate.....
4. Diploma.....
5. Degree.....
99. Not sure

5.18. Religious affiliation of secondary caregiver (tick only one most applicable) **(Chitendero chenyu ndechipi?)**

1. Apostolic (specify which one).....
2. Catholic
3. Protestant (specify which one).....
4. Pentecostal (specify which one).....
5. Atheist
6. Traditional
7. Moslem
8. Others (specify).....

5.19. For how long has the secondary caregiver lived with the child?.....Years and months
(Magara nemwana uyu nguwa yakareba zvakadii?)

6. Child demographic information. (if not sure put code 99)

6.1. Age..... years **and**.....months

6.2. Sex

1. Male
2. Female

6.3. Religious affiliation of child (circle only one most applicable) **(Chitendero chemwana ndechipi?)**

1. Apostolic (specify which one).....
2. Catholic
3. Protestant (specify which one).....
4. Pentecostal (specify which one).....
5. Atheist
6. Traditional
7. Moslem
8. Others (specify).....

6.4. Is the child currently in school?

1. Yes (has been to school in grade one and above in the past 14 days)
2. Yes (has been in preschool in the past 14 days)
3. No (has not been to school for more than 14 days)

6.5. Level of education (*Encircle applicable*) **(Mwana arimugwaro ripi kana kuti akasvika gwaro ripi?)**

Level	None	Grade								Form						Tertiary
Sub-level		0	1	2	3	4	5	6	7	1	2	3	4	5	6	
Code	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

6.6. What type is the child's usual place of residence? (**Mwana anowanzogara kupi? Inzvimbo yakadii?**)

1. Urban
2. Rural
3. Semi-Urban (growth point)
4. Commercial farming community
5. Mining community
6. Squatter camp

SECTION D. SOCIO-ECONOMIC INFORMATION

7. Socio-economic information of child

7.1. Has the child lost any parent? (**Paneumwe wevabereki wemwana akashaya here?**)

1. Yes	Go to Q 9.4
2. No	Proceed to next Q

7.2. If yes which parent has the child lost? (**Ndimai here kana kuti ndibaba?**)

1. Father
2. Mother
3. Both parents

7.3. When was the last parent lost? (**Vakashaya kekupedzisira vakashaya rini?**)

1. Less than a year ago
2. 1-2 years back
3. 2-5 years back
4. more than five years back

7.4. Which parent is surviving?

1. Both
2. Father
3. Mother
4. None

7.5. How old is the head of the household in which the child lives? Years
(**Munhu ari musoro wemba inogara mwana ane makore mangani ekuzvarwa?**)

7.6. Has the child changed households **since birth**? (Staying in another household for a period of more than 6 months)
(**Mwana akambobva mumhuri yaigara achienda kundogara mune imwe mhuri here kubva pakuzvarwa kwake?**)

1.	Never changed households
2.	Changed households once
3.	Changed households twice
4.	Changed households three times
5.	Changed households more than three times

7.7. Has the child changed the primary caregiver in the past 12 months (**Mwana akambosandura munhu anova aripanyanga panyaya dzekumuchengeta here?**)

1. Yes
2. No

7.8. What is the total number of children **under 18 years** staying in the same household?
(**Vana varipasi pemakore gumi nemasere vanogara mumhuri (muimba) imwe nemwana vangani?**)

7.9. What is the total number of people staying in the same household as the child?
(**Muimba inogara mwana mune vanhu vangani vese pamwe chete?**)

7.10. How many times do you eat meat or fish per week? (**put code 99 if not applicable e.g. vegetarian**)
(**Munodya nyama kana hove kangani pasvondo?**)

7.11. How many meals did the child have yesterday?
(**Mwana akadya rungani nezuro?**)

7.12. What are your perceptions on the nutritional adequacy of the diet in your household? (Nutritional adequacy both quantitative and qualitative) (**Sekuona kwenyu, kudya kwenyu kuneutano hwakadii?**)

1. very poor
2. poor
3. average
4. good
5. very good

7.13. Give your reasons for answer to the above question (**Sei muchadaro?**)

.....

.....

.....

SECTION E: ELEMENTS OF THEORETICAL MODELS ON BEHAVIOUR CHANGE

8. Beliefs about medicines including ARVs (Selected items from the Beliefs about Medicines Questionnaire (BMQ) and additional items specific to this study)

How do you rate the following statements on a five point scale? (**Ikozvino ndichaverenga mashoko (kanazvirewo) anotewera mondiudza kuti munobvumirana nawo here kana kuti kwete, Kana muchibvumirana nawo kana kusabvumirana nawo munondiudza kuti munobvumirana kana kusabvumirana nawo zvakanyanya here kana kuti zviripakati nepakati, musakanganwa kundipaminduro idzi dzakazara, kana musina zvamunofunga pamusoro pazvo munondiudzawo zvakare**). (Dealing with a five point scale in Zimbabwean local language you ask each question in two stages. Firstly whether people agree or disagree or are not sure first. Secondly if they agree do they strongly agree or just agree, and similarly if they disagree with the statement.)

Item No		Strongly agree	Agree	Not sure	Disagree	Strongly disagree
	<i>Specific Items of the Beliefs about Medicines Questionnaire (adapted for use in caregivers of children on ART)</i>					
9.4	The child's life would be impossible without his/her ARV Medication. (Mwana haakwanisi kurarama asingamwi mapiritsi ake emaARV).	5	4	3	2	1
9.5	I sometimes worry about the long term effects of the child's ARV medication. (Dzimwe nguwa ndinoshushikana nekufunga kuti mapiritsi emaARV aya anokwanisa kukanganisa utano hwemwana uyu.)	1	2	3	4	5
9.6	Without his/her medication, the child would be very sick (Dai pasina mapiritsi emaARV aya mwana uyu angadai achirwara zvakanyanya)	5	4	3	2	1
9.9	The child's ARV medicines disrupt his/her life. (Mishonga yemaARV iyi inotomupingaidza pamararamiro ake)	1	2	3	4	5
9.10	I sometimes worry about the child becoming too dependent on his ARV medication (Dzimwe nguwa ndinoshushikana zvikuru nekufunga kuti upenyu hwemwana hucharamba hwakanyanyisa kutsamira pamapiritsi ema ARV).	1	2	3	4	5
	<i>General beliefs on the Beliefs about Medicines Questionnaire (in the original format)</i>					
9.14	People who take medicines should stop their treatment for a while every now and then. (Vanhu vanomwa chero ipi zvayo mishonga vanofanira kumborega kumwa mishonga iyi apo neapo kwechinguvana vachizodzokera zvawo pakuimwa)	1	2	3	4	5
9.15	Most medicines are addictive. (Mishonga mizhinji inoita chijairira sechefodya zvokuti hauzodi kuirega)	1	2	3	4	5
9.16	Medicines do more harm than good. (Mishonga inotonganganisa muviri zvakanyanya kudarika kubatsira kwainoita)	1	2	3	4	5
9.17	All medicines are poisons. (Mishonga yese zvayo yakangoita semuchetura)	1	2	3	4	5
9.21	The child's health has improved a lot since he/she started ARVs. (Utano hwemwana uyu hwaita zvirinani zvikuru kubvira paatanga kumwa mapiritsi ema ARV)	5	4	3	2	1
9.22	There has not been much change in the child's health since starting ARVs. (Hapana shanduko yambonyanyisa kuoneka pamwana uyu kubva paatanga kumwa mapiritsi ema ARV .)	1	2	3	4	5
9.25	Traditional medicine is a lot better in treating AIDS than ARVs. (Mishonga yechivanhu inotobatsira vanhu vane AIDS kudarika mapiritsi ema ARV)	1	2	3	4	5

9. Environmental (external) factors

(Dealing with a five point scale in Zimbabwean local language you ask each question in two stages. Firstly give a three-point scale response with not sure in the middle followed by; “a little bit or a lot?” for either of the responses at each end to give a five-point scale. e.g. Easy, difficult or not sure, followed by “extremely easy or some what easy”?, for a response that says it is easy.

Item	Scoring				
	5 (Zvakanyanya)	4 (Zvishoma)	3 (Handiziwe)	2 (Zvishoma)	1 (Zvakanyanya)
10.1How friendly are the health care workers to your child? (Vashandi veutano vanorapa mwana vanoratidza ushamwari hwakadii nemwana?)	Extremely friendly	somewhat friendly	Not sure	Somewhat unfriendly	Extremely unfriendly
	(Vanoratidza ushamwari)			(Havaratidze ushamwari)	
10.2How friendly are the health care workers to you when you bring your child for treatment? (Vashandi veutano vanorapa mwana uyu vanoratidza ushamwari hwakadii nemi kana mauya nemwana?)	Extremely friendly	somewhat friendly	Not sure	Somewhat unfriendly	Extremely unfriendly
	(Vanoratidza ushamwari)			(Havaratidze ushamwari)	
10.3How clear are the health care workers instructions on how to give your child medication? (Vashandi vanorapa mwana uyu vanotsanangura zvinonzvisisika zvakadii pamusoro pemamwirwo anoitwa mapiritsi nemwana)	Very clear	Fairly clear	Not sure	Somewhat unclear	Very unclear
	(Vanotsanangura zvinonzvisisika)			(Havatsanangure zvinonzvisisika)	
10.4How fast are the services offered to you? (Ko rubatsiro rwamunowana pamunouya poga poga runokasika zvadini?)	Very fast	Somewhat fast	Not sure	Somewhat slow	Very slow
	(Runokasika)			(Runononoka)	
10.5How easy is it to get ARV drugs for the child from health facilities? (Zvirinyore sei kuti muvane mapiritsi emwana ema ARV kubva kuzvipatara)	Very easy	Somewhat easy	Not sure	Somewhat difficult	Very difficult
	(Zvirinyore)			(Zvakaoma)	
10.6What is your overall impression about the services that are provided by the health care workers on your child’s health condition? (Rubatsiro rwamunovana pano rwese zvarwo munoruona sei?)	Excellent	Good	Not sure	Poor	Very poor
	(Rwakanaka)			(Haruna kunaka)	
10.7How affordable is transport money to bring your child for treatment? (Mari yekuti mukwire zvifambiso zvinomuunzai kuchipatara irinyore zvakadii kuiwana?)	Very affordable	Somewhat affordable	Not sure/not applicable	Somewhat expensive	Very expensive
	(Irinnyore kuwana)			(Yakaoma kuiwana)	
10.8How easy is it to get transport to bring the child for treatment? (Zvirinyore zvakadii kuvana chekufambisa kuuya kuchipatara nemwana?)	Very easy	Somewhat easy	Not sure/not applicable	Somewhat difficult	Very difficult
	(Chirinyore kuchiwana)			Chakaoma kuchiwana	
10.9How is your relationship with the child? Ukama hwenyu nemwana uyu kwakana kana kushata zvakadii.	Excellent	Good	Not sure	Poor	Very poor

10. Social Support

Tell me how frequent did each of the following statement applied to you in the past 30 days

Ndiudzeiwo kuti zvinhu zvinotewera zvakaitika kwamuri kakawanda zvakadii. Minduro dzamunondipa dzinofanira kupinda muzvikamu zvinoti nguva dzose, nguva dzakavanda, nguva dziripakati nepakati, nguva shoma kana kuti hazvina kumboitika.

<i>In the past 30 days..... Mumazuwa anemakumi matatu apfuura (mu mwedzi wapfuura kubva zuva ranhasi).....</i>	Always (Nguva dzose)	Most of the time (Nguva zhinji)	Half the time (Nguva dziripakati nepakati)	Less of the time (Kashoma kenguva)	Never (Hazvina kumboitika)
10.1. I received help on my daily duties (general chores) (Ndakawana rubatsiro pamabasa angu emazuva ese)	4	3	2	1	0
10.2. I received professional counselling on caring for the child on ART. (Ndakapangwa mazano nevakadzidzira basa rekupanga mazano pamusoro pekuchengeta mwana arikumwa mishonga yema ARV)	4	3	2	1	0
10.3. I discussed with/spoke to, other caregivers of children on ART about caring for the child (Ndakakurukurawo nevamwe vane vana varipamishonga yema ARV pamusoro pekuchengeta vana ivava).	4	3	2	1	0
10.4. I discussed with/ spoke to, other adults about caring for a child on ART (Ndakakurukurawo nevamwe vechikuru pamusoro pekuchengeta vana varipamapiritsi ema ARV)	4	3	2	1	0
10.5. I was reminded by the child to give him/her ARV medication (Ndakatondedzwa nemwana kuti nguva yake yekumwa mapiritsi yakwana)	4	3	2	1	0
10.6. I was reminded by someone in my household to give the child his/her ARV medication (Ndakatondedzwa neumwewo munhu wemumba medu kuti ndichipa mwana mapiritsi emaARV)	4	3	2	1	0
10.7. I received help from someone else in giving the child his/her ARV medication (Ndakavana rubatsiro kubva kuneumwe munhu pakupa mwana mapiritsi ake ema ARV)	4	3	2	1	0

11. Self-efficacy

Item	Score*				
<i>How confident are you that you can give your child his/her antiretroviral medication everyday at the required times?(Munevimbo yakadii yekuti munogona kupa mwana mapiritsi ake ema ARV mazuvaose panguva dzinotarisirwa?)</i>	0	1	2	3	4
11.1. If the child is in good health.(Kanyangwe mwana achiratidzika kuwa neutano)					
11.2. If the child was travelling (Kunyangwe mwana ari parwendo)					
11.3. If there was no adequate food for the child to eat (Kunyangwe pasina kudya kwakakwana kwekuti mwana adye)					
11.4. If the child was feeling ill (Kunyangwe mwana achirwarisa)					
11.5. If it means giving medication in front of people who do not know that the child is HIV positive (Kunyangwe zvichirewa kuti mupe mwana mishonga pamberi pevanhu vasingazivi kuti mwana ane utachivana hwe HIV)					
11.6. If the child was nervous or irritated (Kuntangwe mwana asina kugadzikana achiratidza kushatirwa)					
11.7. If the medicine was hard for the child to swallow (Kunyangwe mwana achitambura kuti amedze mapiritsi)					
11.8. If the child had to change the times they ate (Kunyangwe zvichirewa kuti mwana asandure nguva dzaanodya)					
11.9. If the child had to change the times they slept (Kunyangwe zvichirewa kuti mwana asandure nguva dzaanorara)					
11.10. If the medicine had a bad test or strong smell (Kunyangwe mushonga uinemunhuwi vakasimba kana kuti uchishata kana kuvava mumuromo)					
11.11. When there is no one to remind you (Kana pasina munhu angakutondedzai kuti muchipa mwana mushonga vake)					
11.12. Even if doing so interferes with your daily activities (Kunyangwe kupa mwana mushonga sezvinotarisirwa nguva dzose kuchikangaidza mabasa enyu emazuva ose)					
11.13. When your daily works finish late (Kana mabasa enyuepazuva achinonoka kupera)					
<i>How confident are you that you can carry out the following tasks?(Munevimbo yakadii yekuti munogona kuita zvinotewera)</i>					
11.14. Get the child's medication from a health facility before it runs out (Munotoro mushonga wemwana kuchipatara umwe usati vaperi)					
11.15. Give the child medication as required until s/he is an adult (age may be a confounder) (Muchapa mwana mushonga sezvinotarisirwa mazuva ose kusvikira avamunhu avakukwanisa kuzvimirirawo)					
<i>How confident are you that you can keep your child's antiretroviral therapy appointments at the clinic/ hospital even if..... (muvimbo (munekhwadi) yakadii kuti muchaindisa mwana kuchipatara nguva dzose dzaanenge achitarisirwa kuenda kunyangwe.....)</i>					
11.16. Transport fares are unaffordable (Mari yechifambiso kana isasakwanisiki kuvanika)					
11.17. Transport is hard to get (Chekufambisa chacho kana chichinetsa kuwana)					
11.18. I had to walk with the child for long distances (age and clinical conditions may be confounders here).(Kana zvichirewa kuti ndinofanira kufamba rwendo rwakareba netsoka)					

*Scoring: 0=I definitely will not be able to, 1=I do not think I will be able to, 2=do not know, 3=I think I will be able to and 4=I definitely will be able to

SECTION F: HEALTH AND CARE INFORMATION

12. Care and carer information

- 12.1. Who is responsible for administering the medications? (**Ndiani anebasa rokupa mwana mushonga?**)
1. Primary caregiver solely responsible
 2. Child study participant solely responsible
 3. Child study participant and primary caregiver jointly
 4. Child study participant, primary caregiver and secondary caregivers
- 12.2. Was the child told/ Does the child know that he/she is HIV positive? (**Mwana anoziva/akaudzwa here kuti aneutachivana hweHIV?**)
1. Yes
 2. No
- 12.3. Have you disclosed the child's HIV status to anyone else apart from health workers? (**Pane here umwezve munhu vamaudza kuti mwana aneutachivana kunze kwevanorapa mwana kuchipatara?**)
1. Yes
 2. No
- 12.4. Who is this person to you (use the respondent's perception of close and distant)? (**Munhu uyu ndiani wenyu**)
1. Close Relative
 2. Close Friend
 3. Distant relative
 4. Distant friend
 5. Others (specify).....
- 12.5. Are you on any chronic medication? (**Imi munemishonga yamunogara muchimwa here?**)
1. Yes
 2. No
- 12.6. Have you been tested for HIV? (**Imi makamboongororwa utachivana hweHIV muropa renyu here?**)
1. Yes
 2. No
- 12.7. If yes what was the result? (**..... makavanikwa makadii?**)
1. Positive
 2. Negative
 3. Not sure
- 12.8. If positive are you currently taking ARVs? (**.....murikumwa mapiriti emaARV here?**)
1. Yes
 2. No
- 12.9. Does the child remind you when it is time for him/her to take medication? (**Mwana anokutondedzai kuti muchimupa mairitsi ake emaARV here?**)
1. Always
 2. Sometimes
 3. Never
- 12.10. Is there someone else who reminds you that it is time to give medicine to the child? (**Imi pane munhu anokutondedzai kuti muchipa mwana mushonga here?**)
1. Always
 2. Sometimes
 3. Never
- 12.11. Does the child take medication on his/her own without being reminded? (**Mwana anomwa mushonga asina amutondedza here?**)
1. Always
 2. Sometimes
 3. Never
- 12.12. Apart from people what else reminds you that it is time to give your child medication? (**Panechimwe chinhu chinomutondedzai kuti michipa mwana mairitsi ake here?**)
1. Alarm clock
 2. Meals
 3. Taking my own medication
 4. Others (specify).....
 5. none

13. Health and treatment information

(Confirm the following information from medical records where applicable mark with an X against all responses that have been confirmed/obtained from medical records)

13.1. How long ago was the child first diagnosed to be HIV positive years and months
(Mwana akatanga kubatwa utachivana hwe HIV riini?)

13.2. For how long has the child been taking antiretroviral drugs ? months
(Ko mwana awe nenguwa yakareba zvakadzi achimwa mapiritsi emaARV?)

13.3. What was the child's baseline CD4 measurement on initiating treatment? count or %
(Mwana akawanika masoja emuviri wake anonzi maCD4 akavanda zvakadzi paakazobva otanga kupiwa mapiritsi ema ARV?)

13.4. How long ago was the child's latest CD4 count? months
(Ko mwana akagumisidza kuverengwa masoja emuviri vake iwo maCD4 riini?)

13.5. What is the child's latest CD4 count? or %
(Akavanikwa akawanda zvakadzi?)

13.6. Has the child been hospitalised before? (Mwana akambopiwa mubhedha/ akamboradzikwa muchipatara here?)

1. Yes
2. No
3. Don't know

13.7. If yes how many times has the child been hospitalised? (.....Kangani?)

1. Once
2. Twice
3. Three times
4. More than three times
5. Don't know

13.8. When was the child last hospitalised (confirm with medical records)? Months ago
(Ndirini apo akagumisira kuradzikwa muchipatara?)

13.9. Does the child currently have any other health condition? (Mwana anezvimwe zvirwere zvaainazvo here?)

1. Yes
2. No

13.10. If yes what is/are the health condition(s)? (.....Ndezvipi?)

13.11.

.....

13.12. ARV regimen	Dosage form	Number of Formulations	Regimen type
1. Stavudine, Lamivudine and Nevirapine	1. Solid	1	1. 1 st line
2. Zidovudine, Lamivudine, Nevirapine	2. Liquid	2	2. 2 nd line
3. Stavudine, Lamivudine, , Efavirenz	3. Both	3	
4. Other.....		4	
.....			
.....			
.....			

- 13.13. Has the child changed the ARV regimen before i.e, changed at least one drug from the combination and **not** necessarily the dosage form (confirm with medical records)? (**Mwana akamboshandurirwa umwe kana yese yemishonga yemaARV yaaimwa here?**)
1. Yes
 2. No
 3. Not sure
- 13.14. If yes what was the reason for changing ARV regimen? (**Chikonzero chekushandirirwa mishonga chaiwa chei?**)
1. Side effects
 2. Non-availability
 3. Resistance
 4. Started TB treatment
 5. Others (specify).....
- 13.15. Has the child changed the dosage forms i.e. liquid to solid or from single to fixed dose combination and **not** necessarily from one brand to another (confirm from medical records)? (**Mwana akamboshandurirwa chimiro chemushonga waaaimwa here sekuti kubva kune wemvura kuenda kune mapiritsi kana kubatanidzirwa mishonga miviri kana mitatu yaaimbomwa yakasiyana muiritsi rimwe?**)
1. Yes
 2. No
 3. Not sure
- 13.16. Reason for changing dosage forms? (**.....Chikonzero?**)
1. Non-availability
 2. Old enough to go on solid dosage forms or the next dose strength
 3. Could not swallow solid dosage form
 4. Started TB treatment
 5. Old enough to go on the next do
 6. Other (specify).....
- 13.17. Has the child ever changed the health facility from which he/she receives ART services? (**Mwana akamboshandura chipatara chaairapwa kubvira paatanga kumwa maARV here?**)
1. Yes
 2. No
 3. Don't know
- 13.18. Has the child ever failed to get ARV drugs at the health centre? (**Mwana akambotadza kuvana mapiritsi ake ema ARV kuchipatara kana kukirinika here?**)
1. Yes
 2. No
 3. Don't know
- 13.19. If yes what action did you take? (**.....Chii chamakaita pamusoro pekushaya uku?**)
1. Bought medicine from private pharmacy
 2. Got medicine from another hospital
 3. Waited until supply was available at the health facility
 4. Other (specify).....
- 13.20. Has the child failed to get ARVs at the health facility in the past three months (the past three review and/or ARV refill visits)? (**Mwana akamboshaya mapiritsi ake ema ARV mumwedzi mitatu yapfuura here?**)
1. Yes
 2. No
 3. Don't know
- 13.21. Has the child ever failed to take some doses of his/her ARVs due to non-availability? (**Mwana akambotadza kumwa mapiritsi ake nekuda kwekumashaya kuchipatara here?**)
1. Yes
 2. No
 3. Not sure

13.22. Is the child on any other medication apart from the antiretroviral drugs (other medication includes cotrimoxazole and any other OI prophylaxis or for any other chronic or acute health conditions)?

(Mwana arikumwa imwe mishonga isisri maARV here? Imwe mishonga inobatanidzira ne Cotrimoxazole kana kuti “Cotri”)

1. Yes
2. No

13.23. If yes what is the medication (Request to see container) ? (**....Ndeipi mishonga iyi**)

☐

1. TB treatment
2. TB prophylaxis
3. Cotrimoxazole prophylaxis
4. Other antibiotics (topical or systemic)
(specify).....
5. Antifungal treatment (topical or
systemic).....
6. Treatment for non-chronic non-infectious health
conditions.....
7. Treatment for chronic non-infectious health
conditions.....
8. Others (specify.....)

Appendix 6: Permission to conduct the study at Harare Children's Hospital

Appendix 6

26 FEB. 2009 (FRI) 08:44 FACULTY-OF-PHARMACY-RHODES-UNIVE 6361205 PAGE 2/2
FROM : Hra Hospital FAX NO. : 002634666449 Feb. 03 2009 01:4 (PM) P1

No. 4 Flame Lily Drive
Bluffhill
Harare

20 November 2008

Harare Central hospital
P O Box ST 14
Harare

Dear Sir

RE: APPLICATION TO CONDUCT A RESEARCH

I am applying for your approval to conduct a study on **ADHERENCE TO PEDIATRICS ARVS** in the Harare Children's hospital.

I am registered for the PHD studies with Rhodes University in South Africa and co-supervised with the University of Zimbabwe Department of Pediatrics as well as the University Victor Segalen Bordeaux 2 through the Institute of Public Health Epidemiology and Development. My contacts in the hospital for this study are Dr Mujuru and Dr Chimhini among others.

Your assistance will be greatly appreciated.

Yours faithfully

Linnet Mugova

Linnet Mugova
Cc: Head of Pediatrics - Harare Hospital
Head of Department - Pediatrics - University of Zimbabwe
Dr Mujuru

HARARE CENTRAL HOSPITAL
CLINICAL DIRECTOR
20 NOV 2008
P.O. BOX ST 14, SOUTHERTON
ZIMBABWE

Approved 26

04 FEB. 2009 (THU) 14:35 COMMUNICATION No. 53 PAGE 2

Appendix 7: Permission to conduct the study at Murambinda Mission Hospital

Appendix 7

Permission to do Adherence study at Murambinda Hosp - Yahoo! Mail

Page 1 of 1



Permission to do Adherence study at Murambinda Hosp

Friday, January 23, 2009 2:12 PM

From: "Glenshaw" <glenshaw@bsatt.com>
To: linnette.mugore@yahoo.com

TO WHOM IT MAY CONCERN,

Permission is hereby granted to Linnette Mugore to pursue a study looking into adherence practice among children at Murambinda hospital.

Yours Sincerely,
Dr Monica Glenshaw MBBCh, Senior Doctor Murambinda Hospital

<http://us.mc464.mail.yahoo.com/mc/showMessage?fid=Inbox&sort=date&order=down...> 2/2/2009

Appendix 8: Approval from Medical Research Council of Zimbabwe

Appendix 8

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrczimshared.co.zw
Website: <http://www.mrcz.org.zw>



Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

MRCZ APPROVAL LETTER

Ref: MRCZ/B/63

Date: 21 October, 2009

Mrs Linnetie Mugore
Number 4 Flame Lilly Drive
Bluffhill
Harare

RE: Adherence to Antiretroviral Therapy Among Children in Zimbabwe

Thank you for the Application for Approval to carry out Research Activity that you submitted for review to the Medical Research Council of Zimbabwe (MRCZ). Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study.

This approval is based on:-

- MRCZ application form
- Study protocol and summary
- Informed consent form, English and Shona versions
- Questionnaire

• APPROVAL NUMBER

: MRCZ/B/63

This number should be used on all correspondence, consent forms and documents as appropriate.

• APPROVAL DATE

: 21 October 2009

• EXPIRATION DATE

: 20 October 2010

• TYPE OF MEETING

: Expedited Review

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted one month before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING:** All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices.
 - **MODIFICATIONS:** Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
 - **TERMINATION OF STUDY:** On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices.
 - **QUESTIONS:** Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrczimshared.co.zw.
 - **Other**
 - Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
 - You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.
- Yours Faithfully

Belera

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE



PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH
Registered with the USA Office for Human Research Protections (OHRP) as an International IRB
(Number IRB00002409 IORG0001913)

Appendix 9: Approval from Rhodes University Ethical Standards Committee

Appendix 9



RHODES UNIVERSITY
Where leaders learn

Rhodes University Ethical Standards Committee, Rhodes University, P O Box 94, Grahamstown, 6140
Tel: +27 46 603 8399 • Fax: +27 46 636 1205 • email: R.Jobson@ru.ac.za

BY EMAIL

16 July, 2009

To: Professor R. Dowse, Ms L. Mugore

Research Proposal 2009Q1-3: Adherence to antiretroviral therapy in children in Zimbabwe

This proposal was approved in principle, pending satisfactory responses to queries and concerns, at a meeting of the Rhodes University Ethical Standards Committee on 18 March, 2009.

The queries have been satisfactorily answered, and approval is hereby granted.

Yours sincerely,

M.R. JOBSON
Chairperson: Rhodes University Ethical Standards Committee

**Appendix 10: Letter of Support from the Ministry of Health and Child Welfare,
Zimbabwe**

Appendix 10

23/07/2023 09:09 0124293433
263-04-792981/730192-4

ECONOMICS

MINISTRY OF HEALTH
AND CHILD WELFARE
P O BOX CY1122
CAUSEWAY
ZIMBABWE

Telfax No:
E-mail : atp.director@ymail.com


ZIMBABWE
AIDS AND TB PROGRAMME

7th April 2009

The Clinical Directors
- Harare Hospital
- Murambinda Hospital

STUDY ON ADHERENCE TO ART

This is to confirm that AIDS and TB Unit of Ministry of Health and Child Welfare fully supports Linnetie Mugore, a PAD student at Rhodes University, to conduct a study on Adherence to ART at Harare Children's hospital and Murambinda Mission hospital.

Please give her all the necessary support.

Thank you


DR O MUGURUNGI
DIRECTOR STI/HIV/AIDS & TB
F/MINISTRY OF HEALTH AND CHILD WELFARE


MINISTRY OF HEALTH
TB & AIDS PROGRAMME
07 APR 2009
P O BOX 122, CAUSEWAY
HARARE
COORDINATOR

PLAN ATWE "Wear the Dimple" 2006/2007

Appendix 11: Informed consent form

Page 1 [of 6]

IRB No.

INFORMED CONSENT FORM FOR PARENTAL CONSENT

English version

Adherence to Antiretroviral Therapy in Children in Zimbabwe

Principal Investigator: Linnetie Mugore [B.Pharm (Hons), MPH, PhD Student]

Supervisors: 1. Professor Ros Dowse (Rhodes University, Faculty of Pharmacy)
2. Professor Kusum J Nathoo (University of Zimbabwe, College of Health Sciences, Department of Paediatrics)

What you should know about this research study

- We give you this consent so that you may read about the purpose, risks, and benefits of this research study.
- The main goal of research studies is to gain knowledge that may help future patients.
- We cannot promise that this research will benefit your child. Just like regular care, this research can have side effects that can be serious or minor.
- You have the right to refuse to allow your child to take part, or agree for your child to take part now and change your mind later.
- Whatever you decide, it will not affect your child's regular care.
- Please review this consent form carefully. Ask any questions before you make a decision.
- Your choice to allow your child to participate is voluntary.

Purpose

You are being asked to allow your child to participate in a research study of children who are below the age of 16 years and who are taking the medication that you came to collect today at Harare Children's hospital and Murambinda Mission hospital. The research will be conducted during a period of four weeks.

The purpose of this study is to gather information on children and the medicines they are taking. We hope this will improve the services that children receive at this and other similar health facilities. Your child was selected as a possible participant in this study because s/he is below the age of 16 years and is taking antiretroviral medication and receiving these services at this health facility and if you agree, will be part of an estimated 264 children who will be included in this research study at both Harare Hospital and Murambinda Mission Hospital.

Procedures and duration

If you decide to allow your child to participate, we will ask you some questions about you taking care of the child as well as on the child's health, care and treatment and medication-taking. We will ask your child (if s/he is above the age of 10 years) on how s/he is taking the medication. For this we will use two different tools. All children who will be included in the study will be split into two groups depending on whether we will use a new tool to measure how they are taking their medication, or an old tool that has been used in many other studies similar to this one. This will take about 45 minutes. We may need to get some information from the child's hospital records to complete the information we need for this study.

You may also be asked to take part in group discussions of about 5-6 people. The child you brought today may also be asked to take part in group discussions with other children of his/her age only if s/he is 13 years or older. We will not ask your child to take part in the discussion if s/he has any physical or mental problems that may make it difficult for him/her to participate in the discussion. We will be recording all that is said in the discussion with a tape recorder but all this information will not be disclosed to any persons that are not part of the research team either as audio recordings or written with your names on it. The discussion will take about one hour to 1½ hours. Both the interviews and the group discussions will be done today.

Risks and discomfort

The nature of our study is such that we do not foresee much risk to you and to the child during the course of the interviews and discussions. However we will do our best to protect each adult or child against any form of harm during the group discussions and interviews. There might be some instances where you do not feel free to discuss with a certain person in the same group or some of the questions we may ask cause some discomfort in you or the child. Feel free to tell us (in private) if any of these situations arise during the time we interact with you.

Benefits and/or compensation

You may not individually benefit directly from participating in this study. The information we will collect in this study will help to improve services offered to children in this hospital and other health facilities. We will offer you compensation in the form of transport fares for you and your child within Harare, which will be R20.00. Those who will participate in the group discussions may need to wait longer when others have left and so we will save them with refreshments and give them a little more than the rest, which will be double the transport fares, i.e. R40.00. However, this compensation is in no way an incentive to make you and the child participate in this study and should not bind you to continue participating in this study even when you no longer feel comfortable to do so.

Alternative procedures or treatments

The child will receive the standard care that is due to him/her today and this study will not interfere with, or affect, the services and care that is due to your child today. You and the child have the choice to take part, or not, in this study. Whatever you decide it will not affect your child's regular care.

Confidentiality

Any information that is obtained in connection with this study that can be identified with your child will remain confidential and will be disclosed only with your, and when appropriate, your child's permission. Under some circumstances, the MRCZ and the local Institutional Review Board may need to review patient records for compliance audits. All your details and those of the child will be kept confidential – this means that your name or the child's name will not be on any of our papers used to record the information you tell us in the interviews. We will also not give any information that bears your name to the people treating the child in this hospital or to any person who is not part of our research team. Both the interviews and the group discussion will be conducted in a private place so that other people cannot hear what we say.

We will need to look at your child's health records and we ask you for permission to do this.

In the event of injury

In the event of injury resulting from your child's participation in this study, treatment can be obtained at the Medical Hospitals. You should understand that the costs of such treatment will be your responsibility. Financial compensation is not available.

In the event of injury, contact Mrs Linnetie Mugore, Mobile number: 0912 266 278

Voluntary participation

Participation in this study is voluntary. If you decide not to allow your child to participate in this study, your decision will not affect your or your child's future relations with this institution, its personnel, and associated hospitals and Rhodes University or the University of Zimbabwe. If you decide to allow your child to participate, you and your child are free to withdraw your consent and assent and discontinue participation at any time without penalty. If you do leave the study, we kindly ask you to contact Mrs Linnetie Mugore, Mobile number: 0912 266 278 or any of the other researchers given in the contact section below.

Contact Information**You may contact the following people with any queries and questions about the study****Principal Researcher:**

Mrs Linnetie Mugore.	Rhodes University, Faculty of Pharmacy. c/o University of Zimbabwe, Department of Paediatrics, Harare
	Tel: (04) 791631 (w)
	0912 266 278 (mobile)
	+27 72 864 6497 (South African mobile number)

Other Researchers:

1. Prof R Dowse. Rhodes University, Faculty of Pharmacy, Grahamstown South Africa.
Tel: +27 46 603 8070 (w)
2. Prof K Nathoo. University of Zimbabwe, Department of Paediatrics, Harare
Tel: (04) 791631 (w)

Offer to answer questions

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over.

AUTHORIZATION

YOU ARE MAKING A DECISION WHETHER OR NOT TO ALLOW YOUR CHILD TO PARTICIPATE IN THIS STUDY. YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTOOD THE INFORMATION PROVIDED ABOVE, HAVE HAD ALL YOUR QUESTIONS ANSWERED, AND HAVE DECIDED TO ALLOW YOUR CHILD TO PARTICIPATE.

The date you sign this document to enroll your child in this study, that is, today's date, MUST fall between the dates indicated on the approval stamp affixed to each page. These dates indicate that this form is valid when you enroll your child in the study but do not reflect how long your child may participate in the study. Each page of this Informed Consent Form is stamped to indicate the form's validity as approved by the MRCZ.

Name of Parent (please print)

Date

Signature of Parent or legally authorized representative

Time AM
PM

Relationship to the Subject

Signature of Witness
(Optional)

Signature of Research Staff

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

If you have any questions concerning this study or consent form beyond those answered by the investigator, including questions about the research, your rights as a research subject or research-related injuries; or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe on telephone 791792 or 791193.

Child Assent Form (7-16 years)

My name is..... I am part of a team from Rhodes University in South Africa and the University of Zimbabwe that is conducting a research study on children who are below the age of 16 years and who are taking the medication that you came to collect today at Harare Children's hospital and Murambinda Mission hospital for a period of one month.

This consent form gives you more information about the study. After you have heard what the study is about you can decide if you are happy to take part in the study. Please feel free to stop me and ask questions at any time during my explanation.

The purpose of this study is to gather information on children and the medicines they are taking. We hope this will improve the services that children receive at this and other similar health facilities.

We will ask your caregiver some questions about you, your health, your treatment, your family and the care that he/she provides to you. This will take about 45 minutes. We will ask you (if you are above the age of 10 years) on how you are taking your medication. This we will do using two different tools. All children who will be included in the study will be split into two groups depending on whether we will use a new tool to measure how you are taking your tablets, or an old tool that has been used in many other studies similar to this one. We will also collect some information on your health from your hospital records. You and/or your caregiver may take part in some group discussions about your medication-taking. The discussions will take about 1

We do not think that there can be any harm to you from this study but it may happen that you may not feel good about certain people discussing with you or about some questions that you may be asked. If this happens we ask you to tell us as soon as you can.

We do not promise that you get any rewards through this study. What we find from this study is intended to be used for the benefit of all children who are on the same treatment as you are in hospital that are similar to this one. However you and the adult you came with today may receive a total of R20.00 to help you in your bus fare and this amount will be made double for the children and adults who will participate in the discussions. In addition, these will receive some eats during the discussions.

We will not give anyone who is not part of our study team (including the health staff that are looking after you here) any information collected in this study that bears your name on it.

You have the right to chose to be included in this study or not. You are also free to tell us if you feel that you no longer feel alright to continue taking part in the study. Whatever you decide it will not affect your regular care.

Did you understand well what the study is all about? (*explain again if answer is no*) Do you agree to take part in this study?

I have read/listened to the reading of the above information and I understood the information, asked questions which I needed to and agreed to participate. My participation in this research study is voluntary. I will be given a copy of this consent form to keep.

Name of child:

Age..... years

Signature of minor or initials _____ Date dd / mm / yyyy

Researcher/Research Assistant

I have discussed this research with the guardian and the child using language which is understandable and appropriate. I believe I have fully informed this participant and his/her guardian of the nature of the study and what it involves. I believe the participant and his/her guardian understood this explanation and consented/assented to participate in the study. I swear that all information obtained during this research study will remain strictly confidential.

Name of researcher.....

Signature of researcher_____Date dd... /mm.... /yyyyy.....

Name of Witness.....

Signature of Witness_____Date dd / mm / yyyy

Appendix 12a
Adherence to Antiretroviral Treatment in Children in Zimbabwe

FOCUS GROUP DISCUSSION GUIDE

Caregivers

Tell me your experiences in caring for a child on ART

What are your experiences with ensuring that the child takes his/her medication everyday on time?

What makes it easy and what makes it challenging for you to ensure that the child takes his/her medication everyday on time?

How do you remember to give the child medication everyday on time?

How does it work between you and the child with regard to the child having his/her medication everyday on time?

Who takes responsibility for this role?

How does the child's age affect his/her medication taking?

What are your experiences telling the child that s/he is HIV positive and that she needs to take lifelong medication?

What age do you consider to be ideal for disclosing to the child that s/he is HIV positive

What are your experiences with reporting missed doses to the health facility?

When the child misses taking some of his/her medication as required, how easy is it to report to the health care workers that the child missed some doses?

Appendix 12b

Adherence to Antiretroviral Treatment in Children in Zimbabwe

FOCUS GROUP DISCUSSION GUIDE

Children

Tell me your experiences with taking your antiretroviral medication?

How do you feel about taking medication each day?

What makes it easy and what makes it challenging for you to take your medication everyday on time?

How do you remember to take medication everyday on time?

How does role of taking medicines work between you and the person who cares and ensures that you take medication everyday on time?

Who is responsible for this role?

How does the relationship of this person to you affect your taking of medication daily on time?

Who told you about your health condition (HIV) that you are taking this medication for?

What do you think about reporting to nurses that you did not take some of your medicine, when this happens?

When you have missed taking some of your medication as required, how easy is it to tell the health care workers, when you come to the clinic, that you missed some doses?