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INYUVESI YAKWAZULU-NATALI

Adherence to ARVs in a rural paediatric cohort

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Supervisor: Dr Tanuja N. Gengiah

14 November 2015

SUPERVISOR DECLARATION

As the candidate's supervisor I, Dr Tanuja N. Gengiah, agree to the submission of this dissertation.

Signed: 

Date: 14 November 2015

DECLARATION

In fulfilment of the requirements of the coursework degree of Masters in Pharmacy in the Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Chanelle Smith, declare that:

1. The research reported in this dissertation, except where referenced, and is my original work.

2. This dissertation has not been submitted to UKZN or any other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.

3. This dissertation does not contain other persons' text, tables, data, graphs or other information, unless specifically acknowledged as being sourced from other persons.

4. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then: -
    a. their words have been re-written but the general information attributed to them has been referenced;
    b. where their exact words have been used, their writing has been placed inside quotations marks, and referenced.

5. Where reference to a publication for which I am a principal author is made, I have referenced the "In Press" publication.

6. That my contribution to the project was as follows:

    6.1 Literature Review

    I started in 2014 with the literature review by using PubMed as the primary source for collection of articles. Relevant articles were summarised and included as Table 1 in this dissertation. Review articles were not included in this table even though they may have been referenced in the text.

6.2 Data Collection, clean-up and Analysis

To ensure that the data presented in the manuscript and dissertation was valid and reliable a clean-up of all children's files was conducted. During this process information was updated and verified with Data Management. I conducted demographic tests on SPSS and Graph Pad Prism 6 and created some of the figures used in the manuscript on Graph Pad Prism 6. The statistician conducted all demographic tests, adherence assessments and multivariate analysis in SAS version 3.2.

6.3 Write up of Manuscript

I took overall responsibility for writing the manuscript before submitting a final draft for review and comments to all co-authors. Approval for the final version of the manuscript was received from the four co-authors before submission to the journal. The manuscript was submitted to Turnitin to verify for originality on the 30th of October 2015.

6.4 Submission of Manuscript to Journal

The manuscript was submitted for review and publication to AIDS & Behav on 2 November 2015.

6.5 Write up of Dissertation

I took overall responsibility for writing the dissertation before submitting a final draft to my supervisor, Dr Tanuja N Gengiah, for review and final approval. The final dissertation was submitted to Turnitin on 4 November 2015 which was prior to submission to the postgraduate offices.

7. That the contributions of others to the project were as follows:

Tanuja N Gengiah – Supervisor and co-author of the manuscript
Nonhlanhla Yende-Zuma – Statistician and co-author of the manuscript
Michele Upfold – Co- author of the manuscript
Kogie Naidoo – Co-author of manuscript

Signed: 

Date: 14 November 2015

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Then to my dearest husband, Jacques Leonard Smith, thank you for all your patience and support during this two year period. Most of my personal time was spent on writing and you never complained. You are the best husband ever!

I also wish to extend my sincere gratitude and appreciation to any other person whom I have not listed here who have lent their helping hand in this research project.

Thank you,
Chanelle Smith

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ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ARVs	Antiretroviral Drugs
AZT	Zidovudine
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CD4	T–lymphocyte cell bearing CD4 receptor
CRFs	Case Report Forms
D4T	Stavudine
EFV	Efavirenz
FDC	Fixed dose combination
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
iDART	Intelligent dispensing for antiretroviral treatment
LPV/r	Lopinavir / Ritonavir
MEMS	Medication Event Monitoring System
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PAM	Pharmacy Adherence Measures
PEPfAR	President's Emergency Plan for AIDS Relief
PI	Protease inhibitors
PMTCT	Prevention of Mother to Child Transmission
SA NDoH	South African National Department of Health
UNAIDS	The Joint United Nations Program on HIV/AIDS
VAS	Visual Analog Scale
WHO	World Health Organization

ABSTRACT

Background

To achieve viral suppression in children on antiretroviral treatment (ART) optimal adherence is essential. Generally in clinical practice > 95% of the prescribed ART doses should be taken for patients to have an undetectable viral load < 400 copies/ml. Maintaining adherence ≥ 95% in children on ART is not only challenging but difficult to measure. Barriers to optimal adherence may be related to caregiver's factors and child/caregiver forgetfulness, taste of medicine, financial constraints in accessing care and side-effects. Prior research indicates that the validity of adherence information is improved when multiple sources of information are used. However, little information is available on interventions to improve assessment of adherence in HIV infected children on ART.

Objective

The aim of this study was to assess adherence to ART in a rural paediatric cohort, to determine if monthly adherence assessment by pill count is a reliable predictor of virological outcomes and to identify reasons for non-adherence as reported by the children or caregiver themselves at each visit.

Methodology

A retrospective cohort study was conducted using routinely collected data from children enrolled into the CAPRISA 052 AIDS Treatment Program from June 2008 – September 2013 in a rural area of KwaZulu-Natal, South Africa.

Results

A total of 79 children, with a median age of 7.1 years, enrolled into the CAPRISA 052 AIDS Treatment program. Of these, 78 children were initiated on antiretroviral treatment. Monthly adherence by pill count was categorized into high ≥95% and low <95%. Overall median monthly adherence to treatment was 87.8% (interquartile range (IQR): 71.0-99.6%) at month six, 88.9% (IQR: 77.1-99.8%) at month 12 and 90.8% (IQR: 79.1-99.2%) at month 24. The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (n=63) at month six, 86.6% (n=58) at month 12, and 84.5% (n=49) at month 24. Multivariate analysis demonstrated that children with an overall adherence by pill count ≥ 95%, children with a baseline WHO stage 3 or 4, if the primary caregiver was a family member instead of the biological parents and if the primary caregiver was the recipient of any financial grant were significantly associated with adequate viral load suppression (< 400 copies/ml.)

Conclusion

In conclusion, this treatment program demonstrated sustained high adherence to treatment over a two year period, with monthly pill count being a good tool to measure adherence and viral load assessment remaining the gold standard for assessing treatment success.

STRUCTURE OF THE DISSERTATION

This dissertation was written in accordance with the Guidelines for Presentation of Masters Dissertations provided by the College of Health Sciences, University of Kwa-Zulu-Natal, 2015. There is a single reference list in the Vancouver format for references cited in chapters 1 and 4.

The dissertation comprises of the following chapters:

Chapter 1: Introduction highlights the overall research problem and reason for this study with a thorough literature review that was conducted, including table 1 which is a thorough review of the literature summarising the results of 39 studies of adherence to ART in children and provides data on possible predictors for non-adherence and reasons for non-adherence. The aim, hypotheses and objectives addressed in the manuscript are also listed here. This chapter ends with a conceptual framework around adherence for HIV infected children on ART.

Chapter 2: Methods, comprehensively outlines the processes/procedures conducted throughout the CAPRISA 052 AIDS Treatment Program, including the role of the pharmacist, data collection and data management. This section also describes the methodology for the secondary analysis and describes the study setting.

Chapter 3 includes the Manuscript titled '**Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa'** submitted for publication to the journal AIDS & Behavior. It is presented in the required format for that journal and is the final revised submitted version as approved by all co-authors. All objectives and aims of the study were addressed in this manuscript. It also included a detailed outline of my contribution towards the manuscript and the CAP 052 AIDS Treatment Program. Correspondence from the journal after submission can be found in Appendix C.

Chapter 4 discusses the overall conclusion of the study as well as recommendations for clinical practice, the role of the pharmacist and ideas for future research based on these findings.

CHAPTER ONE: INTRODUCTION

CHAPTER 1: INTRODUCTION

1.1 Background and the context for the study

Since the discovery of Human Immunodeficiency Virus (HIV) in the early 1980's, millions of people have either died from this disease or been affected by associated comorbidities. According to the World Health Organisation (WHO) in 2014, 2.6 million children (<15 years) were living with HIV globally, 220 000 children were newly infected with HIV and 150 000 children demised due to Acquired Immune Deficiency Syndrome (AIDS)-related illnesses (1). Sub-Saharan Africa remains the region with the highest number of children living with HIV, with 2.3 million children living with HIV in 2014, and only 30% of these children (age 0 – 14 years) accessing antiretroviral treatment (ART) (2). In South Africa, 360000 children were reported living with HIV in 2013 (3) with only 156700 initiated on ART (4).

ART, which consist of a combination of at least three different antiretroviral drugs (ARVs) taken daily in the treatment of HIV infection. ARVs have not only improved the quality of life of children on treatment but have also decreased the mortality and morbidity rates in HIV infected children. However, for these ARVs to achieve its aim in rapidly decreasing viral load, increasing CD4 cell count and to delay disease progression, adherence to ART is vital (5). Achieving optimal adherence to ARVs (>95% of doses per month ingested) in children is challenging and there is little information or guidance on how to improve, measure or determine adherence. A prospective observational study, which explored the agreement between pill count and viral load in adult patients on ART, found that a 95% cut-off for adherence by pill count had a closer relationship with viral load outcomes than a 90% cut-off (6). A secondary analysis conducted in a South-African paediatric cohort (children < 2years of age) concluded that adherence by medication return of < 85% increased the likelihood of poor viral suppression (7). Therefore it is unclear whether the > 95% cut off is appropriate for paediatric patients.

Different adherence monitoring methods used by other studies in South Africa included self-report by caregivers, medication return assessments, medication event monitoring systems, visual analog scale, and pharmacy refill (8-10). Amongst these methods, medication return has been shown to have a positive correlation with virologic response in children (7, 8).

Factors previously identified that may negatively influence the ability for a child to adhere to lifelong ART can be related to numerous issues such as caregiver, children, healthcare staff and medication (11-13). Health care staff are responsible to ensure quality of patient-care provider relationships and ensure access of care (14). Sustainability of drug supply, relationship between the healthcare provider and the caregiver, and the possibility that the same healthcare provider might not examine you at each

visit are amongst the barriers that healthcare providers face in supporting medication adherence (11). Other barriers identified by healthcare staff are: clinic infrastructure, waiting times, overcrowding and language barriers(15). All of these structural barriers have an impact on the privacy of the patient. Some challenges or barriers to adherence reported by caregivers, patients and clinical staff in previous literature are: social circumstances, disclosure to the child, psychosocial issues, treatment regimen complexities and primary caregiver support (5, 9, 16, 17). Early detection and resolution of these barriers will improve the clinical outcomes of the children on ART. These factors can all potentially negatively impact adherence to ARVs, therefore, reasons for children failing to adhere to their ARV regimens should be monitored, investigated and successful and sustainable interventions are needed (18).

Prior research indicates that the validity and reliability of adherence information is improved when triangulation or multiple sources of adherence measures are used (13, 14, 19). Few studies published clinical outcomes such as viral load suppression and other objectives methods to assess adherence in children. With safety blood monitoring only being done at enrolment, month six and then annually in accordance with the South African National Department of Health Antiretroviral Treatment Guidelines (20), detecting adherence challenges, treatment failure or virologic failure might delay health care staff to intervene and assist with these challenges. The monthly pill count could be designed to collect valuable information which could be incorporated into clinical care as a monitoring tool. If pill count is found to be a reliable predictor of viral load outcomes, non-adherence can be monitored by clinical staff and this early intervention may perhaps limit treatment and virological failures in paediatric patients on ART. This early discovery of potential treatment failure due to poor adherence to medication is essential to maintain good clinical outcomes. Adherence support services should be offered if non-adherence persists to minimize the possibility of having to switch to second line treatment.

This proposed study aimed to assess adherence outcomes for children on ART in a rural setting and determining whether the monthly pill count can be defined as a reliable measure of medication adherence, or as an independent predictor of virological failure where poor rural settings do not have easy access to frequent viral load monitoring.

1.2 Literature Review

Table 1 is a thorough review of the literature summarising the results of 39 studies of adherence to ART in children and provides data on possible predictors for non-adherence and reasons for non-adherence.

1.2.1 Antiretroviral Treatment and Viral load

In South Africa, HIV infected children ART regimens for first line include two nucleoside reverse transcriptase inhibitors (NRTIs), abacavir and lamivudine, and one protease inhibitors (PIs), lopinavir / ritonavir for those children less than 10kg. All other children are treated with two NRTIs, abacavir and lamivudine, and one non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz (20). Second and third line treatment depends largely on the first line treatment received at initiation and clinician and / or specialist decision.

ART aims to rapidly decrease the viral load of a patient, and assist in maintaining an undetectable viral load and increase the CD4 cell count (21) which will then decrease mortality and morbidity rates, prolong and improve the quality of life for these children.

Good adherence has, in previous studies, been identified or recognized as a positive predictor of viral load suppression in children receiving Highly Active Antiretroviral Treatment (HAART) (5, 19, 22-27). Although achieving complete viral suppression in HIV infected children initiated on HAART is possible, maintaining this is still reported as a major challenge (19).

Some possible predictors for virologic failure that have been identified in some studies are non-adherence (5, 23), baseline WHO stage 3 and 4 (28), not having the biological parent as the primary caregiver (18), travelling distance and time to the clinic (18, 23), poor MEMS adherence (29), younger age (23), children on ART for less than one year (30) and low household income (31).

1.2.2 Adherence Measures

The lack of a defined standard measure of medication adherence remains a limitation for all adults, adolescents and children on ART (25, 32, 33). The main aim with measuring adherence in children on ART is to be able to discover virologic and / or treatment failure as soon as possible and to be able to address this immediately to improve the clinical outcomes of these children (34).

To maximize the of adherence data collected and to minimize the over estimation of adherence often caused by self-report bias, suggestions have been made by previous studies to collect adherence data from multiple sources (10, 13, 19, 35, 36). In rural communities, the feasibility and availability of having multiple sources to collect adherence data is challenging and therefore the available sources have to be reliable to ensure that adherence is measured correctly and that good clinical outcomes are being met.

Currently methods being used by different facilities to measure and monitor medication adherence can be classified as direct or indirect measures of adherence (Figure 1) (19, 22).

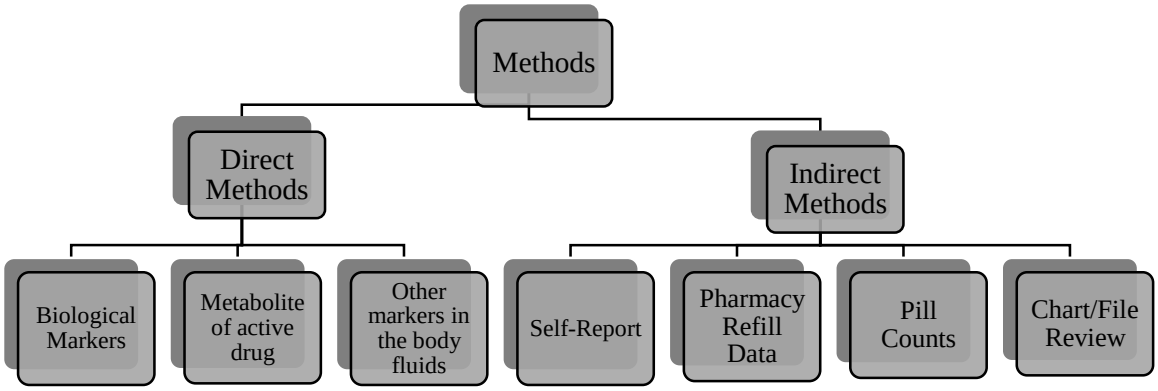

Figure 1: Different methods used for measuring medication adherence

Indirect methods to measure adherence are inexpensive, easily and readily available but they have their own limitations. Pharmacy adherence measures currently being used in practice include pill count, self-report and pharmacy refill data. These measures have been shown to be very reliable predictors of virological outcomes in a resource poor setting (37). Children are often on liquid ART formulations due to difficulty in swallowing tablets, and it is challenging in measuring syrups when dispensed, administered and returned. Self-reported measures including questionnaires and interviews have been considered to be the most practical measure of adherence (14), but detecting poor adherence using self-report is challenging (38). The major limitations contributed by these self-reported measures are recall and social desirability biases. A patient's memory may fail and therefore adherence might be overestimated (39). Liquid formulations are difficult to administer and influence the accuracy of pharmacy refill data (10) as syrups may be spilled during administration, containers may break and there is difficulty measuring correct quantities with syringes.

Medication Event Monitoring System (MEMS), real-time measurement of adherence, has been proven to be useful for calculating adherence but may give underestimated or overestimated adherence results (10), but still remains one of the best methods to measure adherence (33, 40).

Direct methods to assess medication adherence are an objective measure which provides evidence that the patient has actually been taking the drug. The different direct methods available are to detect a drug / metabolite in urine or blood samples, detection of biological markers provided by a specific drug and directly observing whether the patient is taking the drug. These methods are challenging when adherence is assessed quantitatively. Accuracy of these methods are influenced by the half-life of the drug, the metabolism and volume of distribution for each individual patient that may differ (41). These direct methods are also often too expensive, time-consuming and may underestimate adherence results depending on sample timing (42).

1.2.3 Non-Adherence

Non-adherence has been associated with the increase of viral load and decrease of CD4 count (19, 22). It has been highlighted that viral resistance and treatment failure can be attributable to a patient that does not adhere to their prescribed antiretroviral medication regimen dose, time interval and frequency (13).

ART requires commitment from both the primary caregiver and the child. Children may not always understand the reason for being on lifelong ART or what their medication regimen is for (35), so they do not understand the impact that non-adherence may have on the clinical outcomes and quality of life. Some of these children have lost one or both of their biological parents and are then often left in the care of other family members (29). They often then have to rely on their primary caregiver to administer the medication and to take the responsibility of maintaining good adherence to ART medication (10).

As important as it is for the caregiver to take control of the administration of the medication, they themselves might also be ill, elderly or may find it difficult to always be able to keep up with this burdensome responsibility. Elderly caregivers might struggle with administering medication in the form of syrups, dosages may change monthly as the paediatric patient gains weight (Appendix D-I), caregivers may forget what time or what quantity of the prescribed medication should have been given to the paediatric and financially it may not always be possible for them to adhere to the clinic appointment dates, especially if they have to travel far to get to their local clinic or hospital (22).

All of these obstacles emphasize the importance of intervening in this primary caregiver support. We need to understand which barriers for adherence exist for both the primary caregiver of the paediatric and the paediatric, and then aim to find a sustainable solution to this problem. This intervention should be considered to be an ongoing process as the primary caregiver might change over time.

1.2.4 Reasons for non-adherence

Some reasons identified for missing doses in previous studies were reported as: difficult treatment regimens (13), caregiver factors and support (13, 43), psychological issues (44), medication side effects (24), non-disclosure to the child on ARV's (32), pill burden or difficult regimens (24, 45), biological parents not the primary caregiver, communication between primary caregiver and paediatric patient, and the health of the caregiver (36).

Paediatric patients may not always remember, (24, 46) if unsupervised, to take their own medication. They may reject taking medication and also miss doses when vomiting (46).

Most reasons for missing doses are normally collected by self-report (13, 19, 22, 24) and may often lead to recall bias. The paediatric patient or the primary caregiver might not always be willing to admit the truth when they forget to give the medication or cannot always remember if they have missed giving medication dosages to the paediatric patient, they will then give any answer to 'please' the clinical staff. This social desirability bias makes it difficult to understand the context of the problem and formulate a suitable intervention for the reasons for missing doses.

1.2.5 Adherence estimates by pill count / medication return

Clinic pill counts for Zambian children indicated overall median adherence of 96.9%. This cohort had no children with an adherence < 80%. For unannounced home-visit pill count the median adherence was 93.4%, but for this measure 62% children had adherence < 95% and 10% had an adherence < 80% (47). Similarly for children in Uganda adherence estimates for unannounced pill counts / liquid formulations was high with a median adherence of 97.3% (48). Similarly in DarEs Salaam, Tanzania adherence $\geq$95% measured by medication return for all children was 97% (30). In Ethiopia, children part of a cross-sectional study showed poor adherence $\geq$95% (34.8%) by using unannounced home-based pill counts (28).

In South Africa, 79% of children in Cape Town achieved annual medication return adherence >90% and 73% of these children presented with an adherence >95% (8). A longitudinal study in Nyanga, Cape Town, 67% children had an adherence of 100% with returned syrups, this is overestimated when compared to MEMS in this study (10).

1.2.6 Association between viralogic response and adherence by pill count

Few studies have published data on the association between adherence by pill count and virologic response in children. Children in a cross-sectional study in Cape Town, South Africa, suggested that medication return strongly predicted viral response (8). In Zambia at the Macha Hospital, a prospective observational study demonstrated that children with a lower risk of achieving viral suppression were non-adherent to treatment according to pill count (23).

Table 1: Summary of the paediatric ART adherence literature

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Phase i/ii RCT PACTG 377 Multicentre USA sites Children aged 4months – 17years n= 125 (19)	Questionnaires: self-reported by child and caregiver Viral load	64% of children with full adherence achieved an undetectable viral load at their week 48 visit 44% of children with not full adherence achieved an undetectable viral load at their week 48 visit (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	92% Full Adherence for children with a $\geq$2 $\log_{10}$ drop in Viral load 64% Full Adherence for children with a <2 $\log_{10}$ drop in Viral load Overall Full Adherence was reported for 70% and non-FA for 30% of the children	Not available / not done	1. White race 2. Formulation of Protease inhibitor 3. Adherence questionnaire respondent	Poor taste (16%) Patient refusal (16%) for those on ritonavir Complexities of dose scheduling and incorporating with daily lifestyle (10%) taste of nelfinavir (9%)
Qualitative Study, Australia Children 4-14,5 years n= 18 parents (49)	Questionnaire administered to parents, self-report	Not available / not done	89% of families meet required adherence level $\geq$ 95% 11% (all from rural areas) reported low adherence	Not available / not done	Not available / not done	Medication taste (44%) Side effects, vomiting and nausea (44%) Need for medicine preparation (28%)

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Randomized, partially blinded trial Children in the PENTA5 trial n= 266 questionnaires (5)	Questionnaires: self-reported by caregivers	(Undetectable Viral Load defined as viral load < 400 copies/ml)	74% Full Adherence for previous week	1. Non-adherence reported by children	1. Age 2. Caregiver reporting remembering to give ART easily	Difficulty remembering (13%) Interfere with everyday life (31%) Fear of disclosure / social situations Unpleasant characteristics of drugs
Qualitative study Northern Manhattan Children between 3-13 years n= 48 dyads (35)	Self-reported interview with both the caregiver and the child	Not available / not done	Not available / not done	Not available / not done	Not available / not done	Medication missed in last 2 days (8%) Child refused (2%) Medication made child sick (0%) Missed medication last weekend (4%) Missed medication last week (15%) Child has some responsibility for taking medication (56%)
Cross-sectional, descriptive study United States Children < 13years n= 69 caregivers (50)	Pharmacy refill rate	62% children achieved viral suppression (Viral suppression defined as having a viral load < 400 copies/ml)	77% adherence ≥80% 78% overall mean adherence	Not available / not done	1. Income 2. Time on HAART 3. Disclosure Status 4. Caregiver psychological distress	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Retrospective cohort study KZN South Africa, Sinikethemba Clinic Children < 16years n=151 (9)	Self-report of primary caregiver and the child	84% children achieved an undetectable viral load at month 6 80.3% children achieved an undetectable viral load at month 12	59.6% Full Adherence and 27.8% >95% adherence	Not available / not done	Not available / not done	Financial trouble Not re-dosing after vomiting Incorrect dosing Missing clinic scheduled visits and pharmacy refill visits Confusion when multiple caregivers Child refusal Self-discontinuation
Longitudinal Study United States Children 8 – 18 years n= 24 families (51)	Medication Event Monitoring System	Not available / not done	Month 1 - 3: Mean adherence 80.9%, only 17% maintained adherence $\geq$ 90% Month 4 - 6: mean adherence 78.5%, only 21% maintained adherence $\geq$ 90%	1. Better adherence at time 1	1. Degree of responsibility of the child for medication-related tasks 2. Caregiver's regimen knowledge 3. Higher regimen complexities	Not available / not done
Prospective cohort study Cape Town, SA Children 16-61months n= 122 (8)	Medication return Questionnaire	78% Undetectable viral load achieved in those with 90% annual average adherence (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	79% - $\geq$90% adherence by medication return, and of these 73% - >95% adherence	1. Weight- for-height-z-score 2. WHO stage 2 and 3 3. Non-ritonavir containing regime 4. Annual average Medication Return adherence > 90%	Not available / not done	Change in daily routine (12.6%) Secondary education obtained by caregiver Household access to water / electricity Poor palatability (21.8%)

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Retrospective analysis Kigali, Rwanda Children < 15y n=315 (44)	Pharmacy refill	82.8% children achieved an undetectable viral load, and of these 86.8% had complete viral suppression (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	49% had > 95% adherence 46% had 80-95% adherence	Not available / not done	Not available / not done	Not available / not done
Cross-sectional study Addis Ababa Children <3m and <14years n=390 (32)	Questionnaires Self-report Clinical record review Immunological markers	Not available / not done	86.9% adherent in past 7 days 93.1% adherent in past 3 days 96.9% adherent since yesterday 98.2% adherent today	Not available / not done	1. Free treatment available 2. Receiving nutritional support 3. Not on concomitant co-trimoxazole 4. Children unaware of their sero-status 5. Awareness of caregiver health care issues	Child slept (25.5%) Forgetfulness (23.5%) Transport problem (5.9%) Paediatric became depressed (6.9%) Paediatric was ill at the time (2%) Caregiver disbelief in drug (9.8%) Lack of medication / ran out of meds at home (27.5%)
Cross-sectional Survey Lome, Togo, West Africa Children < 15years n= 83 (13)	Interviews with caregivers: Self-report	Not available / not done	42% Overall Perfect Adherence	Not available / not done	1. Sex – females more non-adherent 2. Age above 6years, not knowing HIV status 3. Pill burden 4. ART regimen containing NNRTIs 5. Living in individual housing	Medication out of stock (43%) Forgetfulness (22%) Vomiting (14%) Refusal of child (11%)

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
					6. Caregiver other than biological parent	
Cross-Sectional Study Jamaica Children 18months – 18 years n= 63 children and their caregivers (16)	Self-reported questionnaires Biomarkers (CD4 and viral load)	Mean viral load: 50 cells/ml/10^3 for those in residential care 81.3 cells/ml/10^3 for those in family care	Global adherence 85.7%	Not available / not done	1. Caregiver hours worked 2. Nausea as side-effect of ARVs 3. Age of child	Primarily caregiver related Caregiver forgetting (35%) Caregiver schedule changed (35%) Medication finished (30%) Child travelling away from home (27%)
Clinical Cohort KZN, South Africa Children $\leq$ 15years n= 477 (52)	Not available / not done	Viral Load after 6-12months on Antiretroviral therapy – 73.5% undetectable viral load (Undetectable Viral Load defined as having a viral load < 25 copies/ml	Not available / not done	Not available / not done	Not available / not done	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Quantitative / Qualitative study Urban Lilongwe, Malawi Children < 13 years n= 47 (53)	Focus Group Discussions – self-report Critical Incident Narrative – self-report	Not available / not done	Not available / not done	Not available / not done	Not available / not done	Pharmacy out of stock Financial constraints to purchase medication No reason for no drugs at home Mother daily schedule change Child away from home Child admitted to hospital Child vomited Had visitors
Qualitative study Addis Ababa, Ethiopia n= 12 caregivers n= 14 key informants / health care providers (54)	In-depth interviews with caregivers: self-report	Not available / not done	Not available / not done	Not available / not done	Not available / not done	Pill-burden Fear of stigma and discrimination Transportation challenges due to cost and access ARVs knowledge lacking Economic household problems
Qualitative study Swaziland Clinical Staff n=27 (55)	Questionnaire: Self-report y clinical staff	Not available / not done	4% : 95-100% adherence	Not available / not done	Not available / not done	Daily routine No help to remember Spillage of medicine Forgot Away from home Don’t feel like taking it Don’t want friends asking

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Cross-sectional study New Jersey Children 6-18years n= 46 (36)	1. Caregiver self-report 2. Pharmacy refill 3. Clinic appointment	37% children had and undetectable Viral Load (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	1. 82.6% Full Adherence 2. 60.9% Full Adherence 3. 76.1% Full Adherence 4. Concordance of three measures = 47.8% Full Adherence	1. Concordance of all three adherence measures	Not available not done	Not available / not done
Prospective cohort Latin America multi sites Children and adolescents ≤21years n= 584 (34)	Not available / not done	70% of the children experienced a viral load > 5000 copies/ml WHO guidelines: >5000 vs ≤5000 copies/ml **And** Undetectable Viral Load defined as having a viral load < 400 copies/ml	Not available / not done	1. WHO stage 3 and 4	Not available / not done	Not available / not done
Qualitative study Zimbabwe, 3 rural communities n= 25 nurses n= 8 guardians, age 52 – 79 years (56)	In-depth interviews – self-report by nurses and guardians	Not available / not done	Not available / not done	Not available / not done	Not available / not done	Lack of food Limited disposable income Unable to take child to hospital Poor memory Forget review dates Children remind the guardians Forget dosage and timing of ARVs

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Longitudinal study Nyanga, Cape Town, South Africa Children younger than 7 years n= 53 caregiver-child dyads (10)	1. Medication Event Monitoring System 2. Visual Analog Scale 3. Caregiver 3-day recall 4. Pharmacy refill 5. Measurement of returned syrups	Not available / not done (Undetectable Viral Load defined as having a viral load < 50 copies/ml)	1. 92% Overall adherence /16% >95% 2. 100% Overall Adherence/45% >95% 3. 100% Overall Adherence/43% >95% 4. 100% Overall Adherence/49%>95% 5. 103% Overall Adherence/43%>95%	1. Medication Event Monitoring System	Not available / not done	Not available / not done
Retrospective observational cohort study Limpopo, Rural South Africa Children 8 months – 13 years n= 101 (18)	Not available / not done	74% children achieved an undetectable viral load by the end of the study (Undetectable Viral Load defined as having a viral load < 400 copies/ml after 6 months on antiretroviral therapy) (Undetectable Viral Load defined as having a viral load < 50 copies/ml after 12 months on antiretroviral therapy)	Not available / not done	1. Primary caregiver other than the biological parent 2. Long distances to travel to the clinic, more than 20km 3. Poor adherence on at least one occasion	Not available / not done	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Qualitative Study Democratic Republic of the Congo Children 8-17 years n=20 (29)	In-depth self-reported Interviews Medical chart review	Not available / not done	Not available / not done	Not available / not done	1. Being fed-up with medication regimen 2. Forgetting by both caregiver and children 3. Difficulty with taking medication in secret	No assistance in the home Child does not want to take the medication Clinic appointments repeatedly missed Mistrust in medication High level of curiosity regarding reason for medication
Prospective Study Zambia Children n= 96 (47)	1. Pill counts 2. Caregiver report 3. Visual Analog Scale 4. Medication Event Monitoring System 5. Unannounced monthly home visits	73% Undetectable Viral Load at 48 weeks (Undetectable Viral Load defined as having a viral load < 50 copies/ml)	1. 96.9% median adherence 2. 94.8% median adherence 3. 97.4% median adherence 4. 94.8% median adherence 5. 93.4% median adherence	1. Poor Medication Event Monitoring System	1. Age and Sex 2. Monthly Household income 3. CD4 %	Not available / not done
Prospective observational cohort Macha hospital, Zambia Children <16years n= 267 (23)	Pill count Weight	Month 6 – 88.5% Undetectable Viral Load Month 12 – 88.3% Undetectable Viral Load Month 24 – 77.8% Undetectable Viral Load (Undetectable Viral load defined as	98-100% overall median adherence	1. Non-adherence 2. Longer travel times 3. Age of the child 4. Non-orphan children 5. Using nevirapine at ART initiation	1. Fixed-dose combination antiretroviral drugs	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
		having a viral load < 400 copies/ml)				
Longitudinal sub Study US, multicentre Children and adolescents 8-19 years old n= 120 dyads (17)	Pill count Questionnaire – self-report by caregivers and children	Not available / not done (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	49% children Non-Adherent (adherence < 90%)	Not available / not done	Not available / not done	**By caregiver:** Regimen issues (13%) Child-related issues (25%) Daily routine changed (18%) Child not at home (17%) Child did not want to take the medication (12%) Child feeling well (11%) Busy (11%) **By child:** Regimen issues (29%) Child related issues (33%) Child slept at dose time (28%) Child not at home (23%) Busy (22%) Medication not refilled (21%)
Prospective study Uganda Children 2-10 years n= 121 (48)	Caregiver self-report: 1. 3-day recall 2. 30-day Visual Analog Scale 3. Unannounced pill count / Weight 4. Medication Event Monitoring System	ART at baseline with detectable viral load: Month 6 – 36.7% Month 12 – 38.2% ART initiated at baseline with detectable viral load: Month 6 – 38.5% Month 12 – 25.0% (Undetectable Viral Load defined as	1. 100% median adherence 2. 97.4% median adherence 3. 97.3% median adherence 4. 96.3% median adherence	1. Subjective adherence measures – (Medication Event Monitoring System and Visual Analog Scale)	1. Hospitalization of child in past three months 2. Use of liquid formulations 3. Caregivers use of alcohol	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
		having a viral load < 400 copies/ml)				
Cross-sectional study Ethiopia Children < 15 years n= 210 caregivers (28)	Questionnaire – self-report by caregivers Unannounced home-based pill counts	Not available / not done	93.3% ≥95% adherence for past seven days 34.8% ≥95% adherence	Not available / not done	1. Marital status of caregiver 2. Known HIV status 3. WHO stage3 and 4 more adherent	Caregiver's Forgetfulness (36.4%) Child refusal (27.3%) Lack of food to take with Drug run out at home Child slept Transportation problem Child illness (12.1%)
Cross-sectional Survey South Nigeria Children and adolescents 5 months – 17 years n= 213 dyads (12)	Self-report by caregiver and child / adolescent	Not available / not done	59.2% Full Adherence 76.1% ≥95% adherence	Not available / not done	1. Mother as primary caregiver 2. Age, children less than 5 years more likely to be non-adherent 3. Presence of co-morbidity	Forgetfulness by caregiver (55.2%) Caregiver travelled (25.3%) Caregiver ill (11.5%) Drugs finished (18.4%) Child refused drugs (11.5%) Child slept (9.2%) Child vomited (9.2%) Drugs are too many (6.9%) Child went to school (6.9%) Drugs are bitter (3.4%) No money for transport (2.3%) Family problems (5.7%)
Observational, cross-sectional study Sau Paulo, Brazil	Questionnaire – self-report by child / caregiver	Not available / not done	24hour recall questionnaire – 84.2% Adherence 7 day recall questionnaire – 72.2% Adherence	Not available / not done	1. Medication intolerance 2. Difficulty of administering medication 3. Lower socio-economic class	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Children and adolescents 7-19 years n= 108 dyads (57)	Pharmacy Dispensing Records		54.5% Adherence		4. Missed appointments 5. Lack of virological control 6. Lack of religious practice by caregiver 7. Delegation of responsibility of medicine administration	
Descriptive cross-sectional Dar-Es Salaam Children 2-14years n= 300 (30)	Questionnaire: self-report by caretaker Medication return Nevirapine plasma concentration	Not available / not done	98% adherence ≥95% 97% adherence ≥95% 85% adherence ≥95%	1.Nevirapine plasma concentration 2. Age of patient 3. Patients on antiretroviral therapy for less than 1year 4. Other Infections	Not available / not done	Not available / not done
Cross-sectional survey Ethiopia Children 3months – 14 years n= 193 (58)	Questionnaire / caregiver self-report	Not available / not done	89.1% in last 3 days adherence ≥95% 83.4% in last 7 days adherence ≥95%	Not available / not done	1. Sex ,Males more adherent 2. Age 3. Marital status of caregiver 4. Religion of caregiver 4. Age of caregiver	Caregiver forgot (2.2%) Side-effects (16.3%) Drug ran out at home (2.2%) Chid not at home (5.9%) Lack of privacy (8.1%) Child illness (8.9%) Difficulty in swallowing pills (13.3%) Pill-burden (15.5%) Child depressed (24.4%)

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Cross-sectional Study Northwest Ethiopia Children 2months – 15years n= 314 child caregivers (59)	Caregiver 1month recall self-report 3 day assessment 7 day assessment	Not available / not done	90.4% adherence >95% 98.7% adherence > 95% 96.8% adherence > 95%	Not available / not done	1. Age of the child 2. HIV disclosure to the child 3. Caregiver knowledge of ARV medication	Forgetfulness (52.3%) Medication fatigue (26.2%) Caregiver lack of privacy to administer medication (14.3%) Caregiver illness (11.9%) Other (7.14%) – not at home, transfer related cases, religious beliefs
Prospective cohort study 15 urban sites in US and Puerto Rico Children aged 7 ≤ 16years n= 289 (31)	Self-report medication questionnaire to children and caregivers Viral load	45% children who reported missing 1 dose in past 7 days had a detectable viral load (Undetectable Viral Load defined as having a viral load < 400 copies/ml)	By youth self-report: 28% missed 1 dose in last 7 days By caregiver self-report , 22% missed 1 dose in last 7 days	1. Age 2. Living with biological mother / relative 3. Lower household income 4. Lower estimated caregiver IQ 5. Non-adherence	Not available / not done	Not available / not done
Cross-sectional study Northern Tanzania Children aged 2-17years n= 183 (60)	Pill counts Two-day self-report Visual analogue scale in	Not available / not done	35% Good Adherence 80.9% Good Adherence 73.4% Good Adherence Subjected to all 3 measures – 24.6% Good Adherence	Not available / not done	1. ARV side-effects 2. Missed taking ARVs in six months period 3. Monthly household income 4. Affording transportation to the clinic	Not available / not done

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
Prospective study Western Kenya Children ≤ 14years n=191 dyads (61)	Caregiver self-report Visual Analog Scale by caregiver report Medication Event Monitoring System	Not available / not done	92% Full Adherence 3 Day Recall, and 83% Full Adherence 30 Day Recall 94% Full Adherence 87% mean adherence	Not available / not done	1. Problems in community 2. Problem with giving mediation to child 3. Forgetting to give medication 4. Giving late doses / missing doses	Food insecurity (68%) Transport challenges to the clinic (84%)
Cross-sectional Study Northeast Ethiopia Children 2months – 14years n= 440 dyads (62)	Questionnaires, Face-to-face interviews with caregivers: self-report one month recall	Not available / not done	78.6% had adherence ≥95%	Not available / not done	1. Caregiver substance abuse 2. HIV Status disclosed to the child 3.Caregiver ART knowledge 4. Distance from health facility 5. Caregiver's educational status 6. Current CD4 count is ≥500	Forgetfulness (28.4%) Child refusal (19.3%) Lack of transport (19.1%) Run out of pills (13.2%) Caregiver ill (5.5%) Child ill (3.2%) Pill burden (4.3%) Side-effects (4.3%) Taste of drugs (1.8%) Other (0.9%)
Sub study of open label, RCT Thailand Children 1-12years n= 207 (63)	Announced pill count	13% of the cohort had Viral load Failure over the 144 weeks (Viral load failure defined as having a viral load ≥ 1000 copies / ml)	92% mean adherence before viral load failure for children experiencing viral load failure 98% mean adherence for those without viral load failure 88.3% good adherence	1. Poor adherence by assessed by announced pill count 2. When any challenges to adherence was reported	Not available / not done	Ran out of meds due to delayed clinic visits (29%) Child forgot (21%) Child refused (21%)

Study design/ Country/ Target Population	Adherence Measure	Viral load	Adherence Estimates	Possible predictors for Virological Failure / Suppression	Possible predictors for non-adherence	Reasons for Non-adherence
	Adherence questionnaire – caregiver Child self-report		89.8% (3 day Recall) 84.4% (4 Week Recall)	3. Missed a dose in 24 weeks since last clinic visit		
Cross-sectional Study Five Brazilian centres Children (n=203) and adolescents (n=57) 0-18years n= 260 pairs of children / adolescents and their caregivers (64)	Caregiver self-report when child <13years Adolescent self-report	57% children achieved an undetectable viral load 49% adolescents achieved an undetectable viral load (Undetectable viral load defined as having a viral load < 50 copies/ml)	92.6% Full Adherence reported by children's' caregivers 77.2% Full Adherence reported by adolescents	1. Alcohol/other drugs abuse by caregivers 2. Medication collected from pharmacy – less than 33 days being the median interval	1. Anxiety score less than 8 at HAD of caregivers 2. Children who had HIV diagnosis as a result of family screening	Not done / not available
Qualitative Study South India Children ≤ 12 years n= 14 (11)	Interviews with caregivers	Not available / not done	Not available / not done	Not available / not done	Not available /not done	Side-effects Size of tablets Poor taste of medicine Tablet regimen Taste of medication Child's willingness to take medication Child refusal HIV disclosure

1.3 Problem Statement and Significance of the study

The increased availability of ARVs has rapidly decreased the mortality and morbidity rates of HIV infected children globally. However, the clinical management of any chronic disease relies on the patient being adherent to their prescribed medication. Safety monitoring bloods such as viral load is currently the only reliable determinant for virologic failure, treatment failure and resistance in the treatment of HIV. In rural settings it is not always feasible and sustainable to monitor adherence with safety bloods. A reliable, valid and sustainable measure of adherence for children is crucial in combination with understanding the barriers for non-adherence and to design an intervention that will assist influential factors from the caregiver, child and healthcare workers related to non-adherence.

Achieving optimal adherence to ARV's in a rural paediatric population is challenging but critical to maintain for optimal clinical outcomes. Some of the challenges identified in the literature by caregivers, patients and clinical staff include: forgetfulness, non-disclosure to the child, child away from home, taste of drugs, treatment regimen complexities and primary caregiver support. Prior research indicates that the validity of adherence information is improved when multiple sources of information are used. Few studies have published clinical outcomes (viral load suppression) and other objectives methods (viz. pill count of returned drugs) to assess adherence in paediatrics.

As shown in previous studies and according to the literature review conducted for this dissertation, many studies have collected data on reasons for non-adherence, predictors for virologic failure and non-adherence. However, there is a paucity of information available on interventions to improve assessment of medication adherence in children on ART. There is also a paucity of information on age-appropriate disclosure and the readiness of a child to take responsibility for their own health. HIV has now been classified as a chronic disease where antiretroviral medication needs to be taken for life with good adherence as a key marker for clinical success.

If monthly pill count can be proven to be a reliable predictor of viral load, treatment and virological failure might be picked up by pharmacists or any other clinical team member before the annual monitoring safety bloods are to be done. This will ensure that adherence related barriers or challenges can be addressed and referred for emergent care. This will not only improve the quality of care that children receive, but will also have a positive impact on the quality of life for children on ART.

The current study will assess adherence outcomes using monthly pill counts, viral load along with self-reported reasons for non-adherence.

1.4 Hypothesis

Monthly adherence assessment by monthly pill count, when defined as ≥95%, is a reliable predictor of virological outcomes.

1.5 Aim & Objectives

1.5.1 Aim

The aim of this study is to assess adherence to antiretroviral therapy in a rural paediatric cohort.

1.5.2 Objectives

1. The primary objective of this study is to evaluate the adherence in HIV-infected children in a rural community in KwaZulu-Natal, South Africa on antiretroviral treatment by comparing monthly pill count data with viral load.

2. The secondary objective is to identify reasons for non-adherence as reported by the patients or caregiver themselves on the pill count CRF plate 022.

3. The third objective is to analyse treatment regimens and any single drug or complete switches to determine if virological failure and / or medication side-effects can be linked to non-adherence

1.6 Conceptual framework

Medication adherence is defined as the level to which a patient complies with his / her health care management plan and dosing schedule of any prescribed medicine treatment (12). Traditionally, for a patient to achieve full adherence and maintain good clinical outcomes, the patient has to take more than 95% of the prescribed medication regimen (26, 27).

Defining, measuring and maintaining medication adherence in a paediatric population is a challenge for both the healthcare providing team and the caregivers. Most of the paediatric

patients are taken care of by caregivers other than their biological parents, which results in the caregiver having to take the responsibility to adhere to the antiretroviral treatment program. Therefore the factors influencing the ability of the paediatric to adhere to the prescribed ART regimen can be linked to that of the caregiver (12).

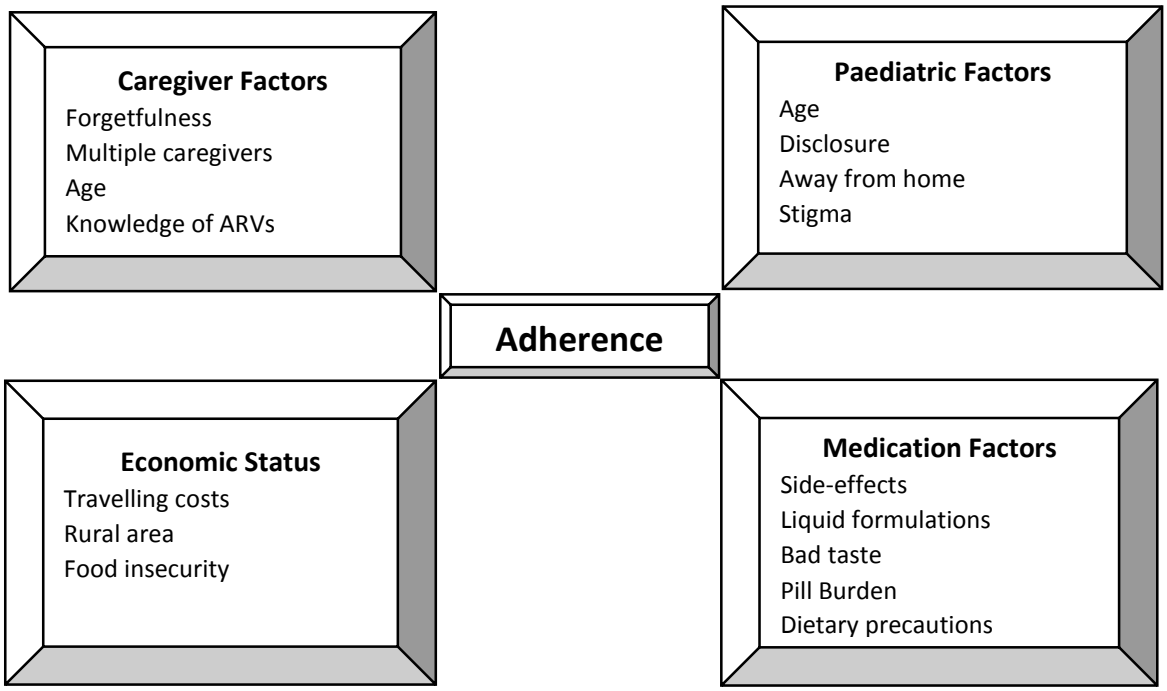

Figure 2: Factors influencing adherence

Caregiver status often changes as elderly caregivers pass away and the paediatric patient are left to be taken care of by another family member or friend (29). This causes confusion as the new caregiver might not have the necessary knowledge on HIV and antiretroviral treatment.

As caregiver of the paediatric patient they do not themselves always understand the disease progression of HIV or the working mechanism of the antiretroviral medication (22, 43).

Paediatric related factors include forgetfulness, not wanting to take the medication, vomiting, running out of medication, non-disclosure, pill burden or feeling self-conscious / uncomfortable to take their ART in front of friends (19, 22, 43, 55).

For the paediatric patient to collect the medication they often have to travel with public transport. Financially this is not always possible and as a result they miss their scheduled appointments and may run out of medication. In rural areas most of the caregivers are

experiencing financial strain, this often can cause food insecurity which may have a negative impact on adherence (43).

Poor taste of liquid formulations or changing the antiretroviral treatment regimen causes the paediatric patient to refuse to take the medication (43). Having to take at least 5 tablets per day is burdensome and difficult to remember. Side-effects caused by the antiretroviral medication is often a fear for the paediatric patient. This leads to them refusing to take the medication.

All of these factors have a negative impact on adherence to antiretroviral medication. To improve the clinical and virological outcomes of the children, these factors need to be addressed.

CHAPTER TWO: METHODS

CHAPTER 2: METHODS

2.1 Study Design

This is a retrospective review of routinely collected data from a paediatric cohort within the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 052 AIDS Treatment Program, for the period of June 2008 – September 2013. However, this study only analysed monthly adherence data by pill count and virologic outcomes for the first 24 months on ART. This study formed part of service provision partially funded by the U.S. President's Emergency Plan for AIDS Relief (PEPfAR).

2.2 Study area

This CAPRISA 052 AIDS Treatment Program was conducted at the CAPRISA Vulindlela Clinic in rural KwaZulu-Natal, South Africa.

2.3 Sample population

Since the inception of the Vulindlela CAPRISA 052 AIDS Treatment Program in June 2008, a total number of 117 HIV infected children (<18years at time of enrolment) were screened for this treatment program, 79 children were enrolled, however only 78 children were initiated on ART during this period and were included in this analysis. The children enrolled into the treatment program were either ARV naïve, treatment interrupted and restarted at the study clinic or on treatment continuation after transfer into the treatment programme from surrounding local clinics.

2.4 Inclusion / Exclusion Criteria

Inclusion Criteria:

Children were initiated on treatment if they met the following inclusion criteria in accordance with national paediatric treatment guidelines operational at the time:

In 2004:

1. Recurrent hospitalisations for HIV-related disease or,

2. WHO stage 2 or 3 disease or,

3. CD4 percentage < 20 for those children <18 months or

4. CD4 percentage <15 for those children ≥18 months.

In 2010:

1. All children <1 year should be started on ART

2. Children 1 – 5 years of age: Symptomatic (stage3 or 4) or CD4 ≤ 25 % or CD4 absolute count < 750 cells/mm3

3. Children ≥ 5 years: Symptomatic (stage III or IV) or CD4 < 350 cells/ mm3

Exclusion: Criteria

Children who received a 052 participant identification number at screening but never initiated on antiretroviral treatment were excluded from this analysis.

2.5 Data Collection

During the five year follow up period of the children enrolled into the CAPRISA 052 AIDS Treatment Program, routinely collected data at each scheduled / unscheduled study visit included: monthly pill counts, self-reported reasons for missing doses, clinical monitoring and safety bloods (CD4 and Viral Load).

Baseline demographics collected at screening included age, gender, WHO staging, previous ART exposure, tuberculosis (TB) status and treatment history, CD4 count, viral load and the ART regimen on which they were enrolled. The type of primary caregiver and parent status were also collected.

Screening and enrolment visits included comprehensive counselling of the primary caregiver emphasizing the reasons for starting ART, accentuating the importance of maintaining adherence, discussion of possible ARV side-effects, responsibility of the primary caregiver, and disclosure. At every monthly visit, weight, height and TB status were collected. Blood samples were collected every 6 months to assess CD4 count, viral load, fasting cholesterol, liver function, glucose and triglycerides. These data were documented on the relevant Case Report Forms (CRFs) and data faxed for safe storage on the CAPRISA data base.

Self-reported measures were used to collect reasons reported for non-adherence and children were requested to return any extra / unused medication at each scheduled / unscheduled visit for completion of the pill count. Using pill count and syrup return data, monthly adherence estimates for each child from enrolment to study exit were collected together with any treatment regimens and / or any single drug or complete switches to determine if virological failure and / or medication side-effects could be linked to non-adherence. Al medication returns whether tablets or syrups are referred to as pill count data in this dissertation.

At enrolment and at monthly follow-up visits the following relevant data were collected on CRFs–

1. Plate #010 Enrolment and Monthly Follow-up (Appendix J): Height and Weight
2. Plate #011 Enrolment and Monthly Follow-up (Appendix K): ART Regimen commencement and changes, reason for any changes, dates of commencement and changes
3. Plate #012 / Plate #022 Pill count (Appendix L & M): Visit date; ARV treatment; Drug Type; Drugs returned, lost or reported as remaining at home; and any reasons for missing doses
4. Plate #013 Laboratory Results (Appendix N): HIV test, CD4 results and Viral Load results

Before the commencement of the CAPRISA 052 AIDS Treatment Program all the relevant CRFs have been validated. The following processes were followed for this validation:

1. All CRFs were designed depending on the type of information required for the CAPRISA 052 AIDS Treatment Program.
2. The CRFs containing laboratory information such as viral loads and CD4 counts were drafted by the data management team and sent to the CAPRISA Vulindlela site and laboratory. This was to ensure and verify that the units were correct for each laboratory variable, that sufficient blocks have been allocated for data to be captured and if skip patterns existed where needed. This was not piloted but assessed at site training before approval of the final set.
3. For behavioural data or data where a response was required the first draft of the CRFs was done by the study team and pharmacy were applicable.

4. At the CRFs training, all other issues with the CRFs were discussed and resolved before edits were finalized.

5. Edit checks were also programmed for certain variables in the Data fax data base to pick up certain obvious errors – like age – if a study is 0 - 18 years only then ages entered above or below this are immediately picked up as Quality Check errors when the forms are faxed in.

Antiretroviral medication was prescribed and dispensed in accordance with the South African National Department of Health (SA NDoH) Antiretroviral Treatment Guidelines (Appendix D-I) for children according to their current weight. If the child sent a relative or sibling to collect their ART due to school attendance, the weight from the previous visit was used. ARV drugs available at the facility included: efavirenz, stavudine, lamivudine, abacavir, didanosine, zidovudine and lopinavir/ritonavir.

At each scheduled / unscheduled study visit the pharmacist documented the quantity of medication returned, quantity of medication reported as lost, quantity of medication reported at home and the quantity of medication dispensed at the current visit on the pill count CRFs. Adherence was calculated monthly during the service provision by using the computerised i-DART (Intelligent Dispensing of Antiretroviral Treatment) program. The i-DART program included the name of the child, date of birth, sex, ART start date, treatment history according to ART active ingredient and a computerised adherence percentage. This calculation took into account the number of days passed since the last clinic visit / ART collection, quantity of medication dispensed at the last visit and the quantity of medication returned at the current visit. The i-DART program also indicated to the pharmacist the amount of medication that had to be dispensed to the child to last till the next scheduled appointment which served as a secondary check for accuracy. This minimized the possibility of children running out of any medication. If by any chance they ran out of medication they were advised to return to the pharmacy for an additional supply to last till their next scheduled appointment.

Monthly adherence support counselling was offered as needed to children and their caregivers when pharmacy adherence calculations by pill count was below 95%. Tools such as pillboxes and cell phone clock reminders were introduced in an attempt to improve adherence with reminders proposed to be set to coincide with a daily activity like a television program or brushing of teeth in the morning. The medication labels included medication instructions in both isiZulu and English. To assist with possible language barriers and to ensure that medication instructions were understood, pharmacy had an isiZulu pharmacist assistant translating

information to the children and their caregivers. Pharmacists also learnt the basic dispensing isiZulu in events where the pharmacist's assistant was not able to assist.

Additional adherence counselling and support was provided if treatment failure was suspected. Treatment failure was defined as having a detectable viral load >1000 copies/ml, tested three months apart, despite good adherence. At this point, children were then switched to an appropriate second line regimen. In accordance with the SA NDoH Antiretroviral Treatment Guidelines in 2004, the limit of detection of viral load was 400 copies/ml. This was subsequently updated in March 2013, in accordance with available test standards, to 50 copies/ml. However, viral load data in this study assessed at months 6, 12 and 24 was based on the limit of detection of 400 copies/ml for consistency.

Any changes to the antiretroviral regimen and reasons for this, were captured on plate #011 (Appendix K) throughout the study and these changes were explained to the children and primary caregivers. Counselling for the updated regimen and the understanding of this regimen and its dosing intervals were emphasized before dispensation.

Children and their caregivers had the knowledge to distinguish between the different ARVs they were taking, its generic names, dosing intervals, colour and shape of tablets and what the medication containers looked like. When they collected medication from other local primary health care clinics, when visiting family in other areas, they were advised to take their empty containers with and verify that the ARVs dispensed to them were exactly the same as the usual. When drugs were received from different pharmaceutical suppliers we informed the children and showed them that the active ingredients were the same. This enabled the children to query any unknown medication received from us or any other clinic.

Efforts to empower the children and enabling them to take the responsibility for their ART outcomes, adherence and overall health were constantly being made by all the pharmacists.

2.6 Data Management

All required CRFs were completed at each scheduled / unscheduled study visit during the five year follow up period of all children initiated on ART. These completed CRFs were data faxed and stored in the CAPRISA data base. This made the data easily accessible for reviewing of completeness, quality and validity.

To ensure validity and reliability of data before commencement of analysis, a full file review of all the participants files have been conducted by the masters' candidate. Any outstanding or incomplete CRFs have been completed and re-faxed.

During the file review, the pill count plate had to be checked / verified for the following:

1. Participant identification number is accurate
2. Date and visit code needs to be filled
3. Ensure that correct treatment code is filled
4. Medication returned, reported at home and dispensed on day of the visit should be filled
5. The drug type should correspond with the quantity of medication dispensed e.g. Drug type 2 = liquid, quantity dispensed cannot be 30, Drug type 1 = tablets cannot be 240.

Safety monitoring bloods, such as VL and CD4, were taken at enrolment, month six, annually and additionally when requested by the study clinician or as per the SA NDoH ART guidelines at the time. Original copies of all safety blood tests were filed in the participant file. This information was captured on an Excel spreadsheet to highlight any missing data. Information mainly included in this spreadsheet were:

1. Participant Identification number,
2. Sex,
3. Date of Birth,
4. Date started on antiretroviral medication,
5. Regimen started on,
6. Any regimen changes including date and reason,
7. CD4% and CD4 count and
8. Viral load results.

The completed excel spreadsheet was sent to the statistician to verify against the CAPRISA data base. After the file review has been conducted, confirmation from the statistician were received that all the relevant information was valid and available for the analyses to start.

2.7 Data Analysis

Statistical Analysis was performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina).

Table 2: Variables for analysis

Variable	Variable Type	Descriptive Measures
Age	Quantitative (Continuous)	Mean with Standard Deviation or Median / Interquartile Range
Gender	Qualitative / Categorical (Nominal)	Frequency
Primary caregiver relation	Qualitative	Frequency
Previous ARV exposure	Qualitative	Frequency
Weight	Quantitative	Mean with Standard Deviation or Median with Interquartile Range
BMI	Quantitative	Mean with Standard Deviation or Median with Interquartile Range
CD4	Quantitative	Median with Interquartile Range
Viral load	Quantitative	Mean with Standard Deviation
Reported challenges	Qualitative	Frequency or Summary
Adherence Monthly	Quantitative	Median with Interquartile Range
Treatment regimens	Qualitative	Frequency
Reasons for missing doses	Qualitative	Frequency

Descriptive statistics were used to describe the baseline characteristics. Baseline demographics included the characteristics of the child; age, gender, WHO staging, previous ART exposure, TB status and treatment, CD4 count, CD4%, viral load and the ART regimen they were enrolled on. The category of primary caregiver and parent status were also collected at enrolment.

Sensitivity and specificity analysis were conducted to check the accuracy of the pill count measure when compared to the viral load measure (gold standard). McNemar's chi-square test for dependent samples was used to determine whether there is a difference in the proportion of high/low adherers when measured using pill count or viral load. Generalised estimating equations were used to identify predictors associated with undetectable viral load (<400 copies/ml) over time. Viral load was categorized into a binary variable (detectable vs. undetectable) and used as a dependent variable. The explanatory variables included in the model were adherence ≥95%, age, gender, WHO stage, whether parent(s) is alive and primary caregiver. These variables were used to assess whether they, predict or influence viral load suppression or detectable viral load. Odds Ratios with a 95% Confidence Interval were calculated in the univariate and multivariate analyses. Variables with an Odds Ratio > 1 or a p-value less than 0.05 were considered to be statistically significant, associated with having an undetectable viral load.

Monthly adherence have been calculated and the average adherence for each patient have been categorized into (high ≥95% and low <95%). For paediatrics who received syrups in their regimen, a leeway of 5% has been added due to difficulty in administrating syrups, wastage/spillage and possible incorrect dosing quantity when syringes were being used.

Adherence percentage for syrup formulations was calculated as follows:

$$\frac{\text{Volume of syrup dispensed at last clinic visit} - \text{Volume of syrup returned at current visit}}{\text{Volume of syrup (ml) that should have been ingested between visits}} \times 100$$

Adherence percentage for tablet formulations was calculated as follows:

$$\frac{\text{Number of tablets dispensed at the last clinic visit} - \text{Number of tablets returned at current visit}}{\text{Number of tablets that should have been ingested between visits}} \times 100$$

The denominator accounts for the time elapsed between clinic visits**.**

2.8 Ethical Considerations and confidentiality

Postgraduate approval and UKZN Biomedical Research Ethics Committee was received before the analyses of this study began (Reference #: BE069/15, E248/05).

The data extracted from the data base for this study was routinely collected in the CAPRISA 052 AIDS Treatment Program which initiated in June 2008. No paediatric patient names were documented on any of the Case Report Forms. Each child received a unique participant identification number at enrolment into the treatment program. That ensured that no linkage

between participant identification numbers and names could be made by the statistician assisting with the analyses. There was no need for informed consent because the data that were used do not contain any identifying patient information and the study was a secondary analysis.

As this was a retrospective cohort study, no incentives were given.

CHAPTER THREE: MANUSCRIPT

CHAPTER 3: ASSESSING ADHERENCE TO ANTIRETROVIRAL THERAPY IN A RURAL PAEDIATRIC COHORT IN KWAZULU-NATAL, SOUTH AFRICA

3.1 Manuscript

Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa

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Running head: Adherence to ARVs in a rural paediatric cohort

Keywords: Paediatric, Children, Adherence, Rural, ARVs

ABSTRACT:

This study retrospectively assessed adherence outcomes using monthly pill count data, viral load data and reasons reported for non-adherence in a paediatric cohort in KwaZulu-Natal, South Africa. Between 2008 and 2013, 78 children, mean age of 7.1 years, were enrolled in the CAPRISA 052 AIDS Treatment Program. Monthly adherence by pill count was categorized into high (≥95%) and low (<95%) categories. Overall median monthly adherence to treatment was 87.8% at month six, 88.9% at month 12 and 90.8% at month 24. The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (63/74) at month six, 86.6% (58/67) at month 12, and 84.5% (49/58) at month 24. Multivariate analysis demonstrated that the baseline WHO stage, primary caregiver status, primary caregiver being the recipient of any financial grant and overall pill count were significant predictors of viral load suppression. In conclusion, this treatment program demonstrated sustained high adherence to treatment over a two year period, with pill count being a good tool to measure adherence and viral load assessment remaining the gold standard for assessing treatment success.

INTRODUCTION

According to the World Health Organisation (WHO) in 2014, 2.6 million children (<15 years) were living with Human Immunodeficiency Virus (HIV) globally, 220 000 children were newly infected with HIV and 150 000 children demised due to Acquired Immune Deficiency Syndrome (AIDS)-related illnesses (1). Sub-Saharan Africa remains the region with the highest number of children living with HIV, with a documented 2.3 million children living with HIV in 2014, and only 30% of these children (age 0 – 14 years) accessing antiretroviral treatment (2). In South Africa, of the 360000 reported HIV infected from 2013 statistics (3), only 156700 were initiated on ART (4).

ART, when taken consistently, aims to rapidly reduce the viral load of patients and the goal of treatment is to maintain an undetectable viral load and to provide sustainable AIDS free survival. (5). Good adherence has in previous studies been identified as a positive predictor of good clinical outcomes and therapeutic success in children, adolescents and adults (6-8). For a patient to achieve virologic suppression and maintain good clinical outcomes more than 95% of the monthly prescribed HIV medication must be ingested (8-10). Whether the $\geq$ 95% cut off is appropriate for paediatric patients is unclear , however a prospective observational study, which explored the agreement between pill count and viral load in adult patients on ART, found that a 95% cut-off for adherence by pill count had a closer relationship with viral load outcomes than a 90% cut-off (11). A secondary analysis conducted in a South-African paediatric cohort (children < 2years of age) concluded that adherence by medication return of < 85% was associated with an increased likelihood of poor viral suppression. (12).

Although comprehensive treatment guidelines are available in South Africa, achieving optimal adherence to ART (>95% of doses per month ingested) and maintaining virological suppression in a paediatric cohort remains challenging. With viral load assessed every six months or annually as per the National Department of Health Paediatric HIV Treatment Guidelines (13), the emphasis on finding an alternate interim (between viral load monitoring) adherence

monitoring tool, particularly in rural areas, is indispensable. There is a paucity of information and insufficient guidance on how to measure and improve adherence in South Africa for this population.

Different adherence monitoring methods used by other studies in South Africa included self-report by caregivers, medication return assessments, medication event monitoring systems, using visual analog scales, and pharmacy refill data (14-16). Amongst these methods, medication return has been shown to have a positive correlation with virologic response in children (12, 15).

Defining, measuring and maintaining medication adherence in a paediatric population is challenging for both the healthcare provider and the caregivers. Sustaining drug supply of paediatric formulations, the relationship between the healthcare provider and the caregiver, and the possibility that the same healthcare provider might not examine you at each visit are amongst the challenges that healthcare providers face in supporting medication adherence (17). Some children are taken care of by caregivers other than their biological parents (18), which results in the caregiver having to take the responsibility to ensure the child is adherent to antiretroviral treatment. Therefore the factors influencing the ability of the child to adhere to the prescribed regimen is also linked to challenges faced by the caregiver supporting the child (19, 20).

Barriers to adherence identified by caregivers, patients and clinical staff include social circumstances, non-disclosure of HIV status to the child, psychosocial issues, treatment regimen complexities, unpalatable medicine, forgetfulness by either the primary caregiver or the children themselves, medication side-effects, and lack of primary caregiver support (6, 19, 21). These factors can all potentially negatively impact adherence to antiretroviral (ARV) medication and to improve the clinical and virological outcomes of the paediatric patients, these factors need to be assessed, and where necessary, addressed.

Without a standardized measure for medication adherence it is difficult to estimate true adherence in a paediatric cohort. Self-reported measures remain the most common used method to determine adherence, but it mainly relies on patient or caregiver memory and may result in over- estimation of actual adherence (10, 22).

The present study evaluates medication adherence in HIV-infected children on ART in a rural South African setting by comparing monthly pill count data with virological outcomes and identifying reasons for non-adherence as reported by the patients or caregiver themselves at each visit. The aim is to assess adherence outcomes for HIV infected children on ART in a rural community and also to assist in determining whether monthly pill count can be defined as both a reliable measure of medication adherence in this population and as an independent predictor of virological failure to assist in resource constrained rural settings that may not have easy access to frequent viral load monitoring.

METHODS

Study design, setting and participants

This was a retrospective analysis of routinely collected data from a paediatric cohort within the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 052 AIDS Treatment programme, for the period June 2008 to September 2013, in rural KwaZulu-Natal, South Africa. The treatment program, funded by the President's Emergency Plan for AIDS Relief (PEPfAR), offered programmatic HIV care to children as per the current SA National paediatric treatment guidelines. Children were eligible to start treatment if they met the following inclusion criteria: Recurrent hospitalisations for HIV-related disease or, WHO stage 2 or 3 disease irrespective of CD4% or, CD4% less than 20 for those younger than 18 months or CD4% less than 15 for children 18 months and older. The children enrolled into the treatment program were either

ARV naïve, ART treatment interrupted requiring ART re-initiation, or requiring treatment continuation after transfer in from surrounding local clinics.

Data collection

Baseline demographics collected at screening included age, gender, WHO staging, previous ART exposure, tuberculosis (TB) status and treatment history, CD4 count, viral load and the ART regimen they were enrolled on. The type of primary caregiver and parent status were also collected. Screening and enrolment visits included comprehensive counselling of the primary caregiver, emphasizing the reasons for starting antiretroviral treatment through counselling the primary caregiver, accentuating the importance of maintaining adherence, discussion of possible ARV side-effects, responsibility of the primary caregiver, and disclosure. Tools such as pillboxes and cell phone clock reminders were introduced in an attempt to improve adherence with reminders proposed to be set to coincide with a daily activity like a television program or brushing of teeth in the morning.

At every monthly visit, weight, height and TB status was documented. Blood samples were collected every 6 months to assess CD4 count, viral load, fasting cholesterol, liver function, glucose and triglycerides. Additional adherence counselling and support was provided if treatment failure was suspected. Treatment failure was defined as having a detectable viral load >1000 copies/ml, tested three months apart, despite good adherence. At this point, children were then switched to an appropriate second line regimen. In accordance with the South African National Department of Health (SA NDoH) Antiretroviral treatment guidelines in 2004, the limit of detection of viral load was 400 copies/ml. This was subsequently updated in March 2013, in accordance with available test standards, to 50 copies/ml. However, viral load data in this study assessed at months 6, 12 and 24 was based on the limit of detection of 400 copies/ml for consistency. Drug regimen changes and/or single drug switches, for virological failure or medication intolerance respectively, was assessed.

Using pill count and syrup volume return data, monthly adherence estimates were calculated for each patient from enrolment to study exit. All medication returns data, whether tablets or syrups, are referred to as pill count data in this manuscript.

Caregiver or child self-report was used to ascertain reasons for missing doses (patient ran out of pills, clinic ran out of medicine, caregiver status changed, cannot recall, caregiver/patient forgot, caregiver did not supervise, felt too ill, cannot recall/denies missing a dose, unknown/remaining medication not returned at visit, or any other reason). Monthly adherence support counselling was offered as needed to children and their caregivers when pharmacy adherence calculations by pill count was below 95%. For the purpose of this study, monthly adherence by pill count was categorized into high if more than or equal to 95% and low if below<95%. For children receiving syrups in their regimen, a 5% volume margin of error was allowed to accommodate challenges in administrating syrups, wastage/spillage and possible incorrect dosing volume with doses administered orally dosing by syringe.

Adherence percentage for syrup formulations was calculated as follows:

$$\frac{\text{Volume of syrup dispensed at last clinic visit} - \text{Volume of syrup returned at current visit}}{\text{Volume of syrup (ml) that should have been ingested from between visits}} \times 100$$

Adherence percentage for tablet formulations was calculated as follows:

$$\frac{\text{Number of tablets dispensed at the last clinic visit} - \text{Number of tablets returned at current visit}}{\text{Number of tablets that should have been ingested between visits}} \times 100$$

The denominator accounts for the time elapsed between clinic visits**.**

Statistical Analysis

Descriptive statistics were used to describe the baseline characteristics. Sensitivity and specificity were calculated for pill count adherence (≥ 95% vs. <95%) using viral load (<400 vs. ≥ 400 copies/ml) as the gold standard. McNemar's test for dependent samples was used to determine whether there was a difference in the proportion of high/low adherers when measured using pill count and viral load. Generalised estimating equations were used to identify predictors associated with undetectable viral (<400 copies/ml) load over time. The variables included in the multivariate model were adherence age, gender, WHO stage, whether guardian was the recipient of any grant and primary caregiver status. All statistical tests were conducted at a 5% level of significance and analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina).

The Biomedical Research Ethics Committee of the University of KwaZulu-Natal reviewed and approved this study (Reference #: BE069/15, E248/05).

RESULTS

Baseline Demographics and clinical characteristics

Since the inception of the CAPRISA 052 AIDS Treatment Program in June 2008, a total number of 117 children were screened and 79 (<18 years at time of enrolment) were enrolled in the programme with 78 initiated on treatment. The age range for these patients was six months – 13 years. Baseline demographics and relevant clinical characteristics are shown in Table 1.

Adherence by pill count

At programme enrolment and depending on age and weight, 54 children received formulations consisting of tablets and syrups, whilst 24 children received tablet only regimens. The

proportion of children who achieved adherence ≥95% at month six, 12 and 24 was 32.3%, 35.8% and 34.5% respectively. Overall median monthly adherence was 87.8% (interquartile range (IQR): 71.0-99.6%) at month six, 88.9% (IQR: 77.1-99.8%) at month 12 and 90.8% (IQR: 79.1-99.2%) at month 24. Median monthly adherence by pill count remained above 85% throughout the follow up period (Figure 1).

Overall reasons reported for missing doses by either the caregiver present at the visit or the patient themselves were: forgetfulness of the caregiver / paediatric (31.0%), felt too ill (15.0%), caregiver did not supervise (13.4%), cannot recall / denies missing any dose (12.0%), caregiver status changed (8.7%), unknown / remaining medication not returned at visit (8.3%), patient ran out of pills (4.5%), change in daily routine / away from home (4.5%), other (2.4%) and side-effects (0.2%), (Figure 2). Other reasons reported for non-adherence were extra pills in container, child refused to take medication, troubled child, does not want to take syrups and caregiver reports no food at home.

Clinical Response to Antiretroviral Treatment

The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (63/74) at month six, 86.6% (58/67) at month 12, and 84.5% (49/58) at month 24. At the end of the follow-up period three children had died, one between month 0 and six of follow-up, and two between month six and 12 of follow-up. A total of 17 children were transferred out to their local primary health care clinics, during the 24 month period, for ongoing care.

During the two year follow-up period, five children were switched to second line treatment due to treatment failure. Treatment failure for four children was confirmed at their month 12 visit and one child experienced treatment failure at month 24. The overall median adherence for these 5 children at month six, 12 and 24 was 95.1%, 80.3% and 100% respectively. Viral load suppression was achieved after regimen change for all five children, however one child had a

detectable viral load 11 months after the regimen switch due to non-adherence. Three other children had a single-drug switch on first line treatment due to laboratory / clinical toxicity (two were for hyperlactatemia and one for suspected abacavir allergy).

Agreement between adherence by pill count and viral load

Sensitivity and specificity for adherence by pill count and viral load (gold standard) was low. We found that 33.9%, 36.2% and 30.6% of children who were truly adherent by pill count were classified as adherent at month six, 12 and 24 respectively (Table 2).

Predictors of viral load suppression

In multivariate analysis (Table 3) children with an overall adherence $\geq$ 95% were 3.56 times more likely to have an undetectable viral load than those with adherence <95%. Children with WHO stage 3 or 4 were 2.70 times more likely to have an undetectable viral load as compared with those with WHO stage 1 or 2 at enrolment. Where the primary caregiver was a family member other than a biological parent, children were more likely to suppress viral load as compared to when the parent was the caregiver. If the guardian was a recipient of any grant the child was 4.05 times more likely to have an undetectable viral load. Age and gender were not predictive of viral suppression.

DISCUSSION

Our study found that overall adherence measured by pill count remained above 85% throughout a two year follow-up period and good clinical outcomes were achieved in this rural paediatric ART cohort. Children with an overall adherence $\geq$ 95% were nearly four times more likely to have an undetectable viral load. However, in our study, sensitivity of pill count to predict

adherence by using viral load as a gold standard was very low and this may possibly be attributable to the ≥ 95% definition for high adherence. The sensitivity and specificity of adherence measures are significantly influenced by the cut-off points chosen by investigators to define the level of adherence (23). Although, the pill count is an excellent measure for healthcare workers to assess adherence more frequently, the gold standard for assessment of adherence to treatment remains the viral load measurement. This highlights the significant challenges in managing adherence on HIV treatment, where the outcome (viral load suppression) measured months after treatment start is indicative of therapeutic success or failure but a less invasive/expensive real-time measure to accurately monitor treatment remains elusive.

Pharmacy adherence measures such as returned pill count can play an important role in monitoring adherence (24), especially to confirm whether the patient understands their ARV regimen dosing and if good clinical outcomes can be expected in between annual safety bloods being done. However studies suggest that multiple measures, and not pill count alone, should be used to predict adherence to maximize the reliability and validity of data collected (21, 25). A study in New Jersey, USA found an association between virologic response and the concordance of all three measurements of adherence: pharmacy refill, caregiver self-report and clinic appointment data (26). In addition the use of monthly pill count in our setting assisted in identifying adherence related barriers or challenges in between scheduled viral load monitoring bloods enabling these barriers to be addressed by referral for additional care to the counsellors and clinicians. Similarly to us, other rural cohorts in Africa also found a positive association between medications return / pill count and viral load (15, 27).

Early literature suggested that adherence of ≥ 95% should be maintained for a patient to achieve virologic suppression and good clinical outcomes (9), and this percentage is often used in practice when assessing a patients' adherence. However, the association between adherence and virologic response in other studies is not always consistent (7, 10, 26). In our study the proportion of children achieving an undetectable viral load was similar to that of the children at

the Sinikethemba Clinic, in rural Kwa-Zulu Natal where 84% of the children had an undetectable viral load at month six and 80.3% children had an undetectable viral load at month 12 (14). Of the children in a prospective cohort study in Cape Town 78% achieved undetectable viral load (15) and in Kigali, Rwanda, an undetectable viral load was attained for 82.8% children (28). In the Cape Town cohort the percentage of children achieving medication return adherence > 90% was 79%, and approximately 58% of the children achieved an adherence above >95% (15). Another prospective study in Uganda showed that over the 12 months of treatment about 40% of the children consistently had a detectable viral load (29). Alarmingly children from New Jersey had poor virologic response to antiretroviral treatment with not even 40% of the children achieving an undetectable viral load of < 400 copies/ml (26). However, that study only used a single-point measurement for viral load to compare virologic outcomes with adherence. In our study, treatment failure and poor tolerance to ART resulting in drug switches was rare.

An important predictor of having an undetectable viral load in the present study was having WHO stage 3 and 4 at baseline. Similarly, Ethiopian children with baseline WHO stage 3 and 4 were more adherent to their treatment (30) as were children with WHO stage 2 or 3 in Cape Town (15). It is possible that children with a more severe disease and their primary caregivers are more motivated to be adherent to treatment in our setting. In contrast, a South American study demonstrated that experiencing a WHO stage 3 and 4 event during the course of treatment was positively associated with viral load > 5000 copies / ml (31).

Several factors may have played a role in the less than optimal adherence demonstrated by some children in our cohort. Some were on antiretroviral treatment for longer periods than those in other studies (10), and treatment fatigue may have set in. Our adherence data was collected monthly or two monthly as opposed to 3-day and 7-day recall periods utilised in other studies which may be easier to remember (29, 32). Poor adherence by pill count can be influenced by errors in measuring and administering liquid formulations. Caregivers might not be able to

administer the correct quantity, they may not have a syringe available for administration and spillages can happen during administration. Pill dumping in toilets or outside bins at the clinic has occurred, infrequently, at our setting where children deliberately threw extra pills away before visiting the pharmacy in order to appear adherent.

It is important to take into account the influence of the primary caregiver on adherence. In a Cape Town cohort a high percentage (88%) of mother's were the primary caregiver (15) and both parents were alive for 72% of the Zambian children (27) as compared to the 42.9% of children in our cohort that have lost both their biological parents and about half of the cohort having a primary caregiver other than their biological parents. Our children were more likely to have an undetectable viral load if the primary caregiver was not the biological parent. In contrast to our findings, a study in Elandsdoorn in rural South Africa reported that children who did not have a parent as the primary caregiver were more likely to have virologic failure (33). The inconsistent results of the influence of the parent as the primary caregiver on adherence and virologic outcomes should be investigated. It is possible that the biological parents might not always be able to supervise the taking of ART treatment and therefore delegate the responsibility to the child themselves. This highlights the importance of counsellors establishing supportive relationships with caregiver and child, in understanding the child's social circumstances, tailoring counselling messages and facilitating age-appropriate disclosure of the child's HIV status to empower them to eventually take full responsibility for their own health, understanding the implications of poor adherence.

Studies have also shown that the socio-economic status of the caregiver is associated with poor adherence (14, 15, 34, 35). In our study children with caregivers who were the recipients of any grant were more likely to have an undetectable viral load. Similar findings in USA, Zambia and Tanzania showed higher income levels and monthly household income were positively associated with viral load suppression (36-38). Caregivers and children often had to make use of public transport to come to our clinic due to longer travelling distances. If they did not have the

money they missed their appointment dates and only came back once they had the available funds.

Memory aids in our study consisted of weekly pillboxes and cell phone alarm reminders which were set to fit their daily routines. In an Ethiopian study the majority of caregivers (67.1%) reported that they were using their watches as a reminder (30). We assisted our caregivers and children in packing these weekly pill boxes during their visit at the pharmacy, labelling the daily or twice daily pill boxes with sun / moon pictograms, together with setting a cell phone alarm reminder. At the next contact visit they were to return the pill box together with any remaining tablets. However not all children liked the pill boxes as they were concerned it would raise unwanted questions from friends and other family members. In a rural setting the availability of cell phones is limited and when the primary caregiver is not at home at the time when the child has to take the medication, doses could be missed. The child might then be asleep when the caregiver returns home. After identification of this barrier we advised the children to find an alternative reminder, this included a television program or any activity which was repeated daily. This encouraged them to be more responsible for taking their own medication. To maintain continuity of care, the importance of a reliable secondary caregiver and handover of responsibilities when primary caregiver is not around was highlighted as a challenge in our cohort.

In our cohort forgetfulness of the primary caregiver and / or the paediatric was reported as the most common reason for non-adherence, similar to other studies where forgetfulness by the caregiver was also distinctly recognised as a reason for non-adherence (19, 30, 32, 39). Other reasons for non-adherence that were similar to previous findings were that the child felt too ill to take medication, a change in daily routine or child ran out of medication (40, 41). In contrast to other studies, in our study side effects of antiretroviral medication reported as a reason for non-adherence was only 0.19% as compared to 16.3% and 4.3% in Ethiopian studies (40, 41) where side-effects of antiretroviral medication was found to be a predictor of adherence (37). In

our study comprehensive counselling included possible side-effects to expect and were advised to return to the clinic if any of these occurred for further management.

This study has several limitations. HIV disclosure and its correlation with adherence outcomes was not measured in our study. Pharmacy refill data as an adherence measure was not assessed. Not all medication was returned at each of the monthly visits as sometimes relatives were sent to collect medication which may affect accuracy of the adherence assessment. Self-reported reasons for non-adherence are subject to recall bias and a desire to please the provider. In addition, all children and caregivers knew what to expect at the visit which included the pill count and questioning about any discrepancies. However, in a cross-sectional study in Ethiopia the proportion of children achieving an adherence >95% by pill count was similar to ours (34.8% vs. 35.8%) (30). The difference, between our assessment of adherence and that of the Ethiopian study is that we collected monthly adherence data over 24 months, whereas their pill counts were unannounced and based on recall for the past seven days, but with very similar outcomes.

Globally a standard definition for paediatric adherence and a reliable and valid measure of adherence is required for any future studies on paediatric adherence to ART in rural settings. While we used the traditional accepted >95% adherence by pill count cut-point to define high adherers we found that lower levels of adherence still resulted in successful treatment outcomes. Little has been done to investigate sustainable interventions to improve medication adherence for children on ART. These interventions should be cognisant of all the possible factors influencing adherence including medication related factors, healthcare related factors, caregiver related factors and child related factors. Considering these factors, more research is needed to determine the effect that early age-appropriate disclosure in children has on their adherence. Continuous education is needed to make HIV infected children more responsible to take their own medication and where possible, to be less reliant on the primary caregiver.

In conclusion, this treatment program proved that high adherence in a rural paediatric cohort in South-Africa is possible. Secondly, although adherence of ≥95% by pill count was found to be associated with viral load suppression and is a good, relatively easy method to monitor adherence at each contact visit, assessment of viral load is still the best measure of treatment success and cannot be substituted.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest

FIGURES AND TABLES

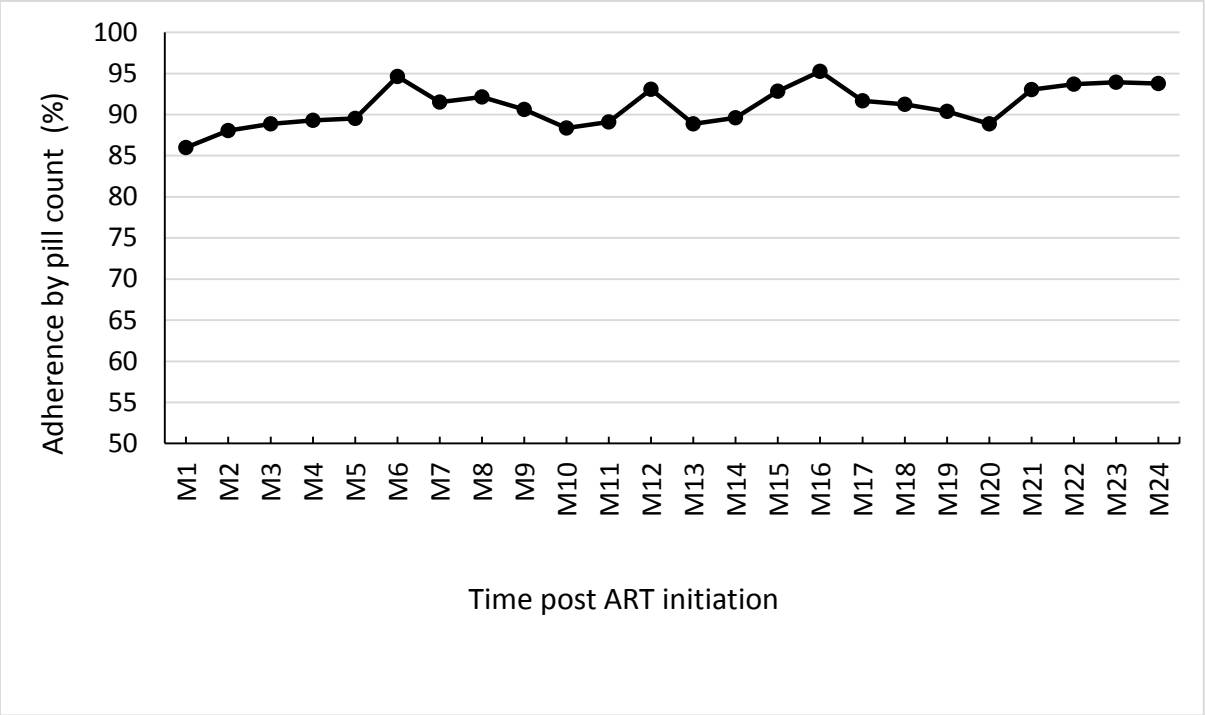

Figure 1: Median adherence over time

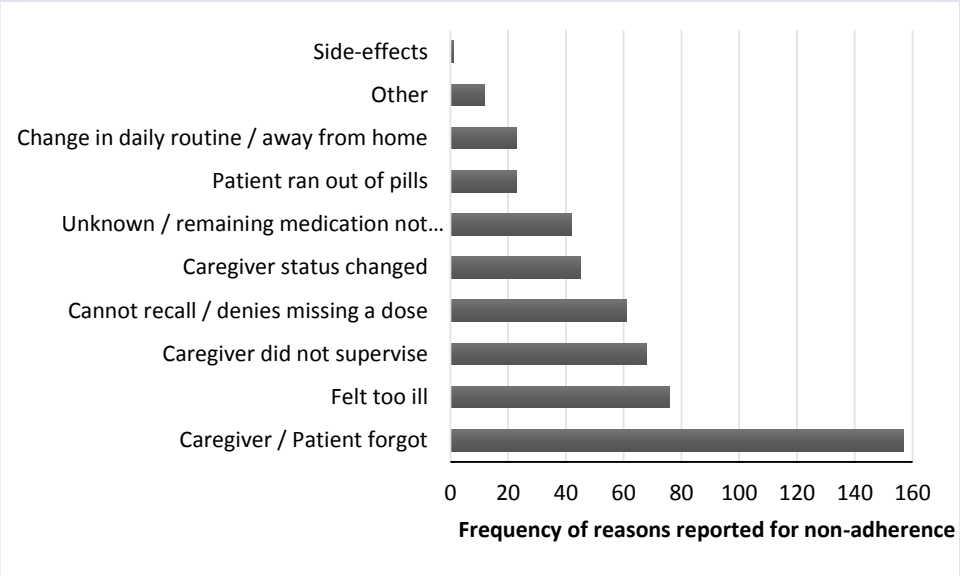

Figure 2: Frequency of reasons for missing doses reported for non-adherence

Table I: Baseline demographics and clinical characteristics

Variable	Overall (N=79)
Demographics	
Age (years), mean ± SD	7.1±3.4
No. of males, %(n)	55.7 (44)
Weight (kg), median (IQR)*	22.0 (17.5 - 26.0)
Which parent(s) alive, % (n)*	
Both	42.9 (33)
Mother only	22.1 (17)
Father only	10.4 (8)
Neither	24.7 (19)
Primary caregiver relationship, % (n)*	
Parent	51.9 (40)
Family member	46.8 (36)
Foster/surrogate parent	1.3 (1)
Social financial support, % (n)*	
Child support grant	69.6 (55)
Foster care grant	6.3 (5)
Disability grant	2.5 (2)
Child support & disability grant	1.3 (1)
No grant	20.3 (16)
ART/HIV information, % (n)	
ARVs initiated in the past*	22.1 (17)
Type of past ARVs, % (n)	
PMTCT	5.0 (4)
Lifelong ART	16.5 (13)
Current TB treatment**	9.2 (7)
WHO stage of HIV disease, *	
stage 1	26.0 (20)
stage 2	28.6 (22)
stage 3	37.7 (29)
stage 4	7.8 (6)
CD4+ count(cells/mm^3), median (IQR)†	278 (126-592)
CD4%, median (IQR)**	12 (5.6-17.5)
Viral load (log copies/mL, mean ± SD‡	4.6±1.2
ART Regimen, % (n)	
EFV/3TC/d4T	47.4 (37)
EFV/3TC/ABC	34.1 (27)
ABC/3TC/LPV/r	8.9 (7)
EFV/3TC/LPV/r HD	8.9 (7)

SD: Standard deviation, IQR: Interquartile Range, ARVs: Antiretroviral drugs, PMTCT: Prevention of Mother to Child Transmission, ART: Antiretroviral Treatment, TB: Tuberculosis, WHO: World Health Organization, EFV: efavirenz, 3TC: lamivudine, d4T: stavudine, ABC: abacavir, LPV/r: lopinavir/ritonavir, HD: half dose

*2 missing data **3 missing data †2 missing data ‡4 missing data

Table II: Agreement between adherence by pill count and undetectable viral load

Adherence by pill count	Viral Load undetectable (<400 copies/ml)		Viral Load detectable (≥400 copies/ml)
Month 6 viral load (N=74)			
≥95%	21 (33.9%)		3 (25.0%)
<95%	41 (56.1%)		9 (75.0%)
Sensitivity		33.9%	
Specificity		75.0%	
Month 12 viral load (N=67)			
≥95%	21 (36.2%)		3 (33.3%)
<95%	37 (63.8%)		6 (66.7%)
Sensitivity		36.2%	
Specificity		66.7%	
Month 24 viral load (N=55)*			
≥95%	15 (30.6%)		4 (66.7%)
<95%	34 (69.4%)		2 (33.3%)
Sensitivity		30.6%	
Specificity		33.3%	

*Pill count data was not available for 3 children at month 24 visit.

Table III: Factors associated with a viral load <400 copies/ml

Variable	Univariate			Multivariate		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Gender (ref=male)						
Female	1.44	0.77-2.70	0.258	1.31	0.63-2.71	0.472
WHO stage (ref=1 or 2)						
Stage 3 or 4	2.90	1.33-6.34	0.008	2.70	1.05-6.92	0.038
Guardian recipient of any grant? (ref=No)						
Yes	3.11	1.52-6.34	0.002	4.05	1.74-9.42	0.001
Primary caregiver (ref =Parent)						
Family member	1.80	0.93-3.45	0.079	3.29	1.52-7.14	0.003
CD4+ count (per 50 cells/mm^3 increase)	1.10	1.04-1.16	<0.001	1.11	1.05-1.17	0.0003
Age (ref:> 7 years)						
≤ 7 years	1.03	0.54-2.00	0.916	1.60	0.68-3.76	0.283
Adherence over time (ref=<95%)						
≥95%	1.99	0.99-3.99	0.052	3.56	1.45-8.77	0.006

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3.2 Discussion of the manuscript

The aim of this manuscript was to assess ART adherence in a rural paediatric cohort and is responsive to all three primary objectives listed in the introduction chapter. The hypothesis driving this analyses was based on monthly adherence assessment by pill count, when defined as >95%, being a reliable predictor of virological outcomes. Descriptive statistics were used to describe the baseline characteristics. Sensitivity and specificity was calculated for high/low adherence to evaluate how well they predicted viral suppression. McNemar's chi-square test for dependent samples was used to determine whether there is a difference in the proportion of high/low adherers when measured using pill count or viral load. Generalised estimating equations were was used to identify predictors associated with undetectable viral (<400 copies/ml) load over time. The variables included in the model were: adherence > 95%, age, gender, who stage, whether parent(s) is/are alive and primary caregiver. Statistical analysis was performed using SAS Version 3.2 (SAS Institute, Cary, North Carolina).

Overall median adherence for all 78 children remained above 85% over the two year follow-up period. The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (n=63) at month six, 86.6% (n=58) at month 12, and 84.5% (n=49) at month 24. Disappointingly, no agreement was found between adherence by pill count $\geq$95% and viral load results. Pill count showed poor sensitivity to predict non-adherence in comparison to viral load. Multivariate analysis showed an association between children with an overall adherence by pill count $\geq$95% and having an undetectable viral load. Multivariate analysis also predicted that children with a baseline WHO stage 3 or 4, if the primary caregiver was a family member instead of the biological parents and if the primary caregiver was the recipient of any financial grant were possible predictors for a child to have an undetectable viral load < 400 copies/ml. The most common reason reported for children to be non-adherent to ART was the caregiver / patient forgot to take treatment (31%).

This study demonstrated sustained high adherence to treatment over a two year period, with pill count being a good tool to measure adherence and viral load assessment remaining the gold standard for assessing treatment success. More research is needed on the influence, importance and role that the primary caregiver has on ART adherence in children. It should also be considered that pill count can be a useful adherence monitoring tool.

Supplementary figures not presented in the manuscript can be found in Appendix O.

3.3 Masters Candidates Contribution to the Journal Article

Student Name: Chanelle Smith

Student number: 214526716

Title of the article: **Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa**

Authors: **C Smith**, TN Gengiah, N Yende-Zuma, M Upfold, K Naidoo

Journal: AIDS & Behaviour

Master student's contribution:

1. Work involved in the CAPRISA 052 AIDS Treatment Program study

I was involved in the dispensing of treatment to all the children enrolled into this treatment program and collecting all pharmacy relevant data. These data included recording the medication returned by the child / caregiver, reasons reported for missing any doses and any concerning adherence data. Counselling of the importance of treatment adherence and possible side-effects to expect was done with the help of a Zulu translator in pharmacy.

2. Formulation of Hypothesis

I contributed to the formulation of the study hypothesis in conjunction my supervisor, Tanuja N Gengiah. I wrote the concept sheet and proposal of this study which was submitted to UKZN Biomedical Research Ethics Committee for approval and ethical clearance.

3. Study Design

I designed the retrospective study with CAPRISA 052 data collected from June 2008 – September 2013.

4. Data Analysis

To ensure that the data presented in the manuscript and dissertation was valid and reliable a clean-up of all the children's file was conducted. I reviewed patients' files and added missing data to the electronic databases. During this process information was updated and verified with CAPRISA data management. I conducted initial demographic tests on SPSS and Graph Pad Prism 6 and created some of the figures used in the manuscript on Graph Pad Prism 6. The statistician conducted all demographic tests, adherence assessments and multivariate analysis in SAS version 9.4 to confirm my initial analysis.

5. Write up

As first author, I took overall responsibility for writing the manuscript before submitting a final draft to all co-authors for review and comments. All the co-authors reviewed and approved the final version of this manuscript which was submitted to the journal, AIDS & Behaviour. The manuscript was submitted for review and publication to this journal on the 2nd of November 2015 (Appendix C). Originality and non-plagiarism was confirmed by submitting the manuscript to Turnitin on the 30th of October 2015.

I declare the above to be a true reflection of my contributions to this journal article.

Signature  Date: 14 November 2015

CHAPTER FOUR: OVERALL DISCUSSION

CHAPTER 4: OVERALL DISCUSSION

4.1 Discussion of major findings

To achieve maximum benefit and optimum clinical outcomes from ARVs, suppressing viral load, improving quality of life, decreasing mortality and morbidity, good adherence to ART is of utmost importance. The aim of this retrospective study was to assess monthly adherence outcomes for HIV infected children on ART in a rural South African community, together with self-reported reasons for non-adherence by the children and primary caregivers. Pill count was compared with viral load to determine whether pill count can be used as a reliable predictor of virologic failure. If the pill count is found to be a possible predictor of virologic outcomes, adherence challenges will hopefully be recognized by the pharmacist long before the child experiences treatment or virologic failure. This would potentially improve the quality of care and improve clinical outcomes for children on ART in the long run.

This study contributed further evidence to findings from previous studies where pharmacy adherence measures, such as pill count, were proven to be useful to monitor adherence and predicted virologic outcomes for children on ART. We demonstrated that good adherence was attainable and virologic outcomes were sustainable over a 24 month period for children in our rural community. Although pill count should be used as an informative monitoring tool in clinical care, we advise that viral load should remain the gold standard to monitor treatment outcomes.

Each objective of this study was met as follows:

4.1.1 Objective 1: To evaluate the adherence in HIV-infected children in a rural community in KwaZulu-Natal, South Africa on antiretroviral treatment by comparing monthly pill count data with viral load

This study found that overall median adherence by pill count for the 78 children throughout the two year follow up period was good and remained above 85% throughout. There was no significant difference in overall median adherence by pill count over time for children considering baseline demographics such as gender, which parent was alive, WHO staging and the primary caregiver status (Appendix O – additional data).

Similar to our findings, other rural cohorts in Africa found a positive association between medications returned /pill count and viral load (8, 23). However, the association between adherence and virologic outcomes in other studies (19, 22, 36) have given inconsistent results. Previous literature suggested that adherence of $\geq$ 95% should be maintained for a patient to achieve virologic suppression and good clinical outcomes (26), and this percentage is often used

in clinical practice when assessing a patient's adherence. Similar results were found with a high proportion of children achieving an undetectable viral load in our study and other studies conducted in South Africa (8, 9) and Rwanda (44). Of the children in a prospective cohort study in Cape Town, 78% achieved undetectable viral load (8) and in Kigali, Rwanda, an undetectable viral load was attained for 82.8% children (44). In the Cape Town cohort the percentage of children achieving medication return adherence > 90% was 79%, and approximately 58% of the children achieved an adherence above >95% (8).

Even though an association was found between adherence by pill count ≥95% and virologic outcomes, the proportion of children having an undetectable viral load with adherence by pill count ≥95% at the three time points in our study showed low agreement. Pill count had a low sensitivity to predict viral load outcomes. Sensitivity, specificity and accuracy of an adherence measure can be influenced by the cut-off points used to define the level of adherence (41). It is evident that the standard definition used in adults, where it is advised to have an adherence ≥95% to achieve virologic suppression, may not be similar for children. With pill count (cut-off 95%) showing poor sensitivity when used cross-sectionally to predict non-adherence in comparison to viral load in our study, we suggest that the gold standard for assessment of adherence to treatment should remain viral load assessment.

Ethiopian children with baseline WHO stage 3 and 4 were more adherent to their treatment (28) as were children with WHO stage 2 or 3 in Cape Town (8). These results are consistent with our study which concluded this is an important predictor for a child to have an undetectable viral load. WHO stages 3 and 4 are both influenced by malnutrition which can lead to poor adherence in children (43). It is possible that children with more severe disease along with their primary caregivers may be more motivated to be adherent to treatment in the setting in which we work.

Pharmacy adherence measures such as returned pill count can play an important role in monitoring adherence (37), especially to confirm whether the patient understands their ARV regimen dosing and if good clinical outcomes can be expected in between annual safety bloods being done. However studies suggested that multiple measures, and not pill count alone, should be used to predict adherence to maximize the reliability and validity of data collected (13, 14). The use of the monthly pill count in our setting assisted us in identifying adherence related barriers or challenges in between viral load monitoring bloods enabling these barriers to be addressed by referral for additional care to the counsellors and clinicians.

Other possibilities for poor adherence by pill count can be attributable to errors such as measuring and administering liquid formulations. Administering the correct quantity of liquids is challenging; caregivers may not always have a syringe available for administration and

spillage can happen during administration. Pill count also relies on the child returning all unused medication at the next scheduled visit which were often not done as children came to the clinic after school or the primary caregiver came alone to collect treatment when the child was away from home. Pill dumping in toilets or outside bins at the clinic has occurred at our setting where children deliberately threw away extra pills before visiting the pharmacy to hide the possibility of non-adherence. This may have over-estimated adherence in our study. Children and their primary caregivers are prone to act in socially desirable ways, as they know that any discrepancies with medication returned will be questioned. The children / primary caregiver should have an understanding that the measures used by pharmacy to monitor adherence are necessary to ultimately improve treatment outcomes.

4.1.2 Objective 2: To identify reasons for non-adherence as reported by the patients or caregiver themselves

Reasons reported for non-adherence were collected by self-report thus, the results may have been impacted by social desirability bias. The reason most frequently reported for non-adherence in our study was forgetfulness of the primary caregiver and / or the paediatric (30.97%). This is similar to other studies where forgetfulness by the caregiver was also distinctly recognised as a frequently reported reason for non-adherence (12, 16, 28, 32). It is pertinent that due consideration be given to the role of the primary caregiver in adherence outcomes for children on ART.

Child felt too ill to take medication, a change in daily routine and child ran out of medication were some other reasons reported for non-adherence in our study and was similar to previous findings (58, 62). All caregivers and children in our study were continuously counselled on what possible side-effects to expect and were advised to return to the clinic if any of these occurred for further management. This may be the reason for the low frequency of side effects of antiretroviral medication (0.19%) reported as a reason for non-adherence in this study as compared to 16.3% and 4.3% in Ethiopian studies (58, 62) and side-effects of antiretroviral medication was found to be a predictor of adherence in Northern Tanzania (60). Educating caregivers and children on side-effects, contra-indications and how their ARVs work to fight HIV should be part of adherence counselling performed by pharmacy.

Information that was not collected in our study was the impact that disclosure could have on adherence. A randomized, partially blinded trial which collected adherence data through self-reported questionnaires by caregivers concluded that the fear of disclosure was a significant reason for non-adherence (5). Caregivers in South India, where none of the children had been

disclosed to and none knew their HIV status, reported that they were concerned about disclosure and the impact it will have once the children are older (11). For HIV infected children, caregivers often choose for their children not to be disclosed to, due to fear for stigmatization (65). It is possible that disclosure of the child's HIV status might reduce stress and improve adherence support, but one has to consider what impact this will have on potential for discrimination and stigma for children. To resolve the challenges introduced by stigma and disclosure, involvement from a multidisciplinary team and support from the community is needed.

4.1.3 Objective 3: To analyse treatment regimens and any single drug or complete switches to determine if virological failure and / or medication side-effects can be linked to non-adherence

Regimen and single / complete drug changes can be related to virologic failure, medication side-effects, clinical toxicity or non-adherence. In our study only four children were changed to second line treatment related to treatment failure at their month 12 visit and one child at month 24 visit. The overall median adherence for all five children at months six, 12 and 24 was 95.1%, 80.3% and 100% respectively. After regimen changes occurred, all five children achieved viral suppression. For one child a detectable viral load was noted 11 months after regimen change due to non-adherence. Little information is available on drug switches related to treatment / virologic failure in paediatric literature. The availability of child friendly ARVs is limited.

In our study, treatment failure and poor tolerance to ART resulting in drug switches were rare. Three children had a single-drug switch on first line treatment due to laboratory / clinical toxicity (two were for hyperlactatemia and one for suspected abacavir allergy). In a Rwandan cohort, 8.3% of the children had to change regimens due to toxicity compared to only 3.8% in our study (44). The low percentage of changes due to clinical toxicities can be related to toxicities being difficult to diagnose by nurses, although all the nurses at our clinic are highly trained and all suspected clinical toxicities are referred to the clinician for follow-up. Continuous education and training of health care professionals is vital and key to provide quality of care.

A major difference between our study and that of others is the association found between age and adherence. Age of the child was a predictor for adherence in the cross-sectional study conducted in Lome, Togo (13), a prospective Zambian study (47) and a cross-sectional South Nigerian Study (12). In the United States, a randomized, partially blinded trial concluded that children above the age of 10 years were likely to be more adherent to their treatment (5),

however this US study did not collect detailed data on the primary caregivers and the sample size of children older than 10 years was small. Similarly, in Jamaica, older children receiving family care were more likely to be adherent (16). Younger children are often more reliant on the primary caregiver to take responsibility for ART adherence as compared to older children who tend to take over this responsibility but then have to possibly deal with stigma and judgemental issues around the mode of acquiring their disease. Children mature at different ages, thus accurate assessment of the child's readiness and capacity to take responsibility for ART should be considered, but the need for children to take the responsibility from an early age might improve treatment outcomes.

The inconsistent results of the influence of the parent as the primary caregiver on adherence and virologic outcomes should be investigated (8, 18, 23). Responsibility shifting of ART is possible when the biological parents are not always able to supervise medication administration due to daily responsibilities. To maintain continuity of care, the importance of a reliable secondary caregiver and handover of responsibilities when primary caregivers are not around were highlighted as a challenge in our cohort and should be investigated. This also highlights the importance of counsellors in understanding the relationship between the child and primary caregiver. Counsellors should consider tailoring counselling messages to improve the relationship between the child and primary caregiver and possibly considering disclosure of the child's HIV status from an early age to empower them to take full responsibility for their own health and to understand the implications of poor adherence.

Other primary caregiver related factors that have been associated with poor adherence are financial difficulties, economic household problems, limited disposable income and the socio-economic status of the caregiver (8, 9, 54, 56). Similar barriers, higher income levels and monthly household income, have also been associated with virologic outcomes in other studies (47, 50, 60). In our study children with caregivers who were the recipients of any financial grant were more likely to have an undetectable viral load. Financial impediments often hinder the children and caregivers to adhere to clinic appointments which ultimately has a negative impact on treatment adherence. In our study children and caregivers often had to make use of public transport to come to our clinic due to longer travelling distances. If they did not have the money for transport, they missed their clinic appointment dates and only came back once they had the available funds.

These findings highlight the challenge for healthcare staff to better understand adherence in children, the effect the primary caregiver has on adherence and the barriers that need to be addressed to improve medication adherence in children on ART. More research should be

conducted with regards to the primary caregiver and the support they need to ensure good adherence and clinical outcomes for their children. Continuous training on paediatric ART adherence should be included at health facilities to ensure that all healthcare staff understand the regimens, dosing strategies and possible barriers faced by caregivers.

To improve adherence, memory aids in our study consisted of weekly pillboxes and cell phone clock reminders which were set to fit the children's daily routines. We assisted our caregivers and children in packing these weekly pill boxes during their visit at the pharmacy, labelling the daily or twice daily pill boxes with sun / moon pictograms, together with setting a cell phone alarm reminder. At the next contact visit they were to return the pill box together with any remaining tablets. However not all children liked the pill boxes as they were concerned it would raise unwanted questions from friends and other family members. In an Ethiopian study, the majority of caregivers (67.1%) reported that they were using their watches as a reminder (28). In a rural setting, the availability of cell phones is limited and when the primary caregiver is not always available or is often away from home when the child has to take the medication, doses could be missed. The child might then be asleep when the caregiver returns home. After identification of this barrier we advised the children to find an alternative reminder, this included coinciding ART dosing with a television program or any activity which was repeated daily. This encouraged them to be more responsible for taking their own medication.

4.2 Study limitations

This study has several limitations. HIV disclosure and its correlation with adherence outcomes was not measured in our study. Not all medication was returned at each of the monthly visits as sometimes relatives were sent to collect medication which may affect accuracy of the adherence assessment. Self-reported reasons for non-adherence are always subject to recall bias and a desire to please the provider. In addition, all children and caregivers knew what to expect at the visit which included the pill count and questioning about any discrepancies. Information on who reported reasons for non-adherence was not collected. This should be taken into inconsideration due to the difference in agreement of self-reported reasons by caregivers and children reported in other studies (17).

4.3 Recommendations for clinical practice

The pill count contains valuable information which could easily be incorporated into clinical care as a monitoring tool. Pill count should be completed at the beginning of the visit before the child is seen by the clinician, nurse or counsellor. This will not only minimize the deliberate possibly ditching of any extra pills before coming to the pharmacy, but will also ensure that early detection of adherence challenges are referred for timeous action. Educating and empowering children to take the responsibility for their own health from an early age including age-appropriate disclosure of their HIV status should be considered and discussed with the primary caregiver before commencement of ART. The mode of acquiring their disease should be taken into account when disclosure is being discussed.

In a multidisciplinary healthcare team, the pharmacist, may play the role of a child's primary adherence supporter as many of the children have often lost family members due to HIV related illnesses. These children are also in desperate need of social support, peer support groups, disclosure guidance and for medical staff to be more sensitive and knowledgeable about each individual's history and treatment management.

The role of the pharmacist in clinical practice should be centred and focussed on improving patient medication adherence. Pharmacists have the necessary medication expertise to improve and minimize non-adherence through patient-contact. Patient specific barriers and challenges should be identified and suitable interventions to overcome these should be discussed in consultation with the patient.

A healthcare team effort is needed to address non-adherence and find future interventions that are children specific and sustainable.

4.4 Recommendations for future research

Globally, a standard definition for paediatric adherence and a reliable and valid measure of adherence is required for any future studies on paediatric adherence on ART in rural settings.

Previous studies have also highlighted methodological challenges when comparing data. The fact that the methods used to measure medication adherence differ across studies (45), recall and social desirability caused by self-report (32) are difficult to account for and the inconsistent results for adherence being a predictor of virologic response (23) are some aspects that need standardisation in paediatric ART care. Furthermore, the appropriate cut-off point to define

medication adherence in children should be investigated and standardization of measures of monitoring adherence should be studied and compiled (46).

Little has been done to investigate sustainable interventions to improve medication adherence for children on ART. Adherence interventions and research need to include the psychosocial influence of HIV (43). These interventions should be cognisant of all the possible factors influencing adherence including medication related factors, healthcare related factors, caregiver related factors and child related factors. Considering these factors, future research should focus more on the effect that early disclosure in children has on their adherence. Both the primary caregiver and paediatrics' ideas, problems and understanding about antiretroviral treatment and adherence should be studied and investigated (17, 35, 44). Suggestions were also made to educate the caregiver and the medical staff about good adherence practices, to make sure relevant people fully understand medication dosing and administration (55). Continuous education is needed to make HIV infected children more responsible to take their own medication and to be less reliant on the primary caregiver. To include the entire family in the treatment process compared to only having one primary caregiver, might add more reliability to the support and treatment outcomes of the paediatric (9).

Even though pill count is readily available in limited resource settings to use as an adherence measure, barriers influencing self-reported reasons for non-adherence / missing doses by primary caregivers or children need to be investigated.

4.5 Concluding statements

Overall adherence by pill count for HIV infected children on ART was good with patients visiting the clinic monthly for treatment collection and clinical follow-up. Increased monthly contact with the children and their caregivers assisted the pharmacist to build a relationship that was more than just a professional relationship. Honesty and trust was emphasized throughout the treatment program. Pharmacists worked in conjunction with other health care staff to ensure quality of care for these children. During the five year follow up period our pharmacy maintained stock levels of three months of medication per patient per ARV and therefore did not experience any medication stock-outs. Treating, managing and following these children during the CAPRISA 052 AIDS Treatment program was a team approach which made it possible to be a great success.

In conclusion, this treatment program proved that high adherence in a rural paediatric cohort in South Africa is possible. Secondly, although adherence of ≥95% by pill count was found to be associated with viral load suppression and is a good, relatively easy method to monitor adherence at each contact visit, assessment of viral load is still the best measure of treatment success and cannot be substituted.

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APPENDICES

APPENDICES

Appendix A: Supervisor / Student Memorandum of Understanding

Supervisor-Student Memorandum of Understanding
Prepared by Prof MJ Chimbari

This memorandum states the responsibilities of the supervisor(s) and postgraduate student and requires both parties to accept the responsibilities by signing.

Details of Student, Supervisors, and Project

Student Name: Chanelle Smith
.....
Student Number: 214526716
.....
School: Pharmaceutical Science
.....
Degree: Masters in Pharmacy (Pharmacy Practice)
.....
Supervisor(s): Dr Tanuja N Gengiah
.....
Research Topic: Adherence to antiretroviral drugs (ARVs) in a rural paediatric cohort
....
Date 29 May 2015
.....

Responsibilities of the Postgraduate Student

While there are many responsibilities carried by a student in pursuing postgraduate studies the following are the minimum expected.

1. Student should identify a research topic acceptable to the supervisor in order to register
2. Student must show commitment to the degree programme and undertake to produce a full proposal within 3 month of registering
3. Student must produce written work that is their best effortt for comments by the supervisor
4. Student should meet at least once per month (in person or through skype) with the supervisor and have the courage to request for such meetings. In all such meetings the student should provide a brief report of their work and take minutes of the discussions and retain such records until the degree has been awarded
5. Students must keep a laboratory manual where all experimental procedures and data are recorded. This laboratory manual remains the property of the university
6. Student must demonstrate the highest level of scientific honesty at all *stages (proposal writing, seeking ethical approval, collecting data, analyzing data and writing thesis or manuscripts)* of the degree programme.
7. Students must familiarize themselves with the university's policy on Plagiarism
8. Students should follow the advice provided by the supervisor and if they choose not to they should discuss the matter with the supervisor immediately
9. Student must always inform the supervisor of their whereabouts
10. Student should keep up to date with literature in their field of study and share any new literature they come across with the supervisor
11. Student must agree to complete studies within the time specified in the CHS handbook for the specific degree programme

12. Student should allow the supervisor to publish their work if they do not do so or show interest one year after graduating on the understanding that the student will be co-author

Responsibilities of the Supervisor

1. Supervisor must support student at all stages of the degree programme *(settling down, proposal writing, ethical applications, data collection, data analysis and write up of thesis or manuscripts)*
2. Supervisor must be sensitive to the overall well-being of the student
3. Supervisor must have good knowledge of the research area of the student
4. Supervisor must be available to the student and should have regular meetings (face to face or by skype) with the student. If the supervisor must be away for an extended period they should identify a co-supervisor to assist the student during that period
5. Supervisor must read work submitted by student for comments and give feedback within 3 weeks depending on the nature of the work submitted
6. Supervisor must be constructively critical to the student's work
7. Supervisor must have sufficient interest in the work of the student
8. In instances of co-supervision the supervisors must avoid confusing the student by giving conflicting opinions/comments. If there are differences in opinion those should be discussed among the supervisors and the student given the agreed opinion.
9. Supervisor should, where funds permit, facilitate arrangements for masters and doctoral students to present a paper or a poster at an international conference as part of training
10. Supervisor must provide an annual progress report on the research and progression of the student to the discipline
11. Supervisor must protect the work of the student by not pre-maturely publishing it or assigning another student to similar work
12. Student must always be the first author of their work and any co-authorship with other people not on the supervision team should be clarified at an early stage of the project

Conflict Resolution

Should there be a conflict or disagreement between supervisor and student which cannot be resolved by the parties involved, then either party can approach the Academic Leader Research or Dean and Head of School (or the College Dean of Research if the Dean and Head of School is one of the conflicting parties) about the conflict. The Dean and Head of School (or College Dean of Research) will then either arbitrate or choose a senior academic of the School not involved in the conflict to arbitrate. The arbitrator's decision is final and cannot be appealed.

Signatures:

Student.....

Supervisor: .....

Academic Leader Research or D&HoS.....

Appendix B: BREC Approval Letter

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

13 May 2015

Mrs C Smith (214526706)
Discipline of Pharmaceutical Sciences
Westville Campus
chanelle.smith@caprisa.org

Dear Mrs Smith

Protocol: Adherence to ARV in rural Paediatric cohort.
Degree: MPharm
BREC reference number: BE069/15

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 09 March 2015.

The conditions have been met and the study is given full ethics approval.

This approval is valid for one year from **13 May 2015.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **09 June 2015.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Appendix C: Response from Journal

Chanelle Smith

From: em.aibe.0.46e78a.1064caff@editorialmanager.com on behalf of AIDS and Behavior (AIBE) <em@editorialmanager.com>
Sent: 02 November 2015 03:04 PM
To: Chanelle Smith
Subject: Acknowledgement of Receipt

Dear Mrs Smith:

Thank you for submitting your manuscript, "Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa", to AIDS and Behavior.

During the review process, you can keep track of the status of your manuscript by accessing the following web site:

http://aibe.edmgr.com/

Your username is: Chanelle Smith
Your password is: available at this link
http://aibe.edmgr.com/Default.aspx?pg=accountFinder.aspx&firstname=Chanelle&lastname=Smith&email_address=chanelle.smith@caprisa.org

With kind regards,

The Editorial Office
AIDS and Behavior

AIDS and Behavior

Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa

--Manuscript Draft--

Manuscript Number:	
Full Title:	Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa
Article Type:	Original Research
Keywords:	Paediatric, Children, Adherence, Rural, ARVs
Corresponding Author:	Chanelle Smith, B.Pharm CAPRISA Durban, KwaZulu-Natal SOUTH AFRICA
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Funding Information:	President's Emergency Plan for AIDS Relief (PEPfAR) (grant # 5U2GPS001350) — Not applicable
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	Columbia University-South Africa Fogarty AIDS International Training and Research Program (AITRP Grant) (D43 TW000231) — Tanuja Narayansamy Gengiah
	the Columbia University-South Africa Fogarty AIDS International Training and Research Program (AITRP Grant) (D43 TW000231) — Kogieleum Naidoo
Abstract:	This study retrospectively assessed adherence outcomes using monthly pill count data, viral load data and reasons reported for non-adherence in a paediatric cohort in KwaZulu-Natal, South Africa. Between 2008 and 2013, 78 children, mean age of 7.1 years, were enrolled in the CAPRISA 052 AIDS Treatment Program. Monthly adherence by pill count was categorized into high (≥95%) and low (<95%) categories. Overall median monthly adherence to treatment was 87.8% at month six, 88.9% at month 12 and 90.8% at month 24. The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (63/74) at month six, 86.6% (58/67) at month 12, and 84.5% (49/58) at month 24. Multivariate analysis demonstrated that the baseline WHO stage, primary caregiver status, primary caregiver being the recipient of any financial grant and overall pill count were significant predictors of viral load suppression. In conclusion, this treatment program demonstrated sustained high

	adherence to treatment over a two year period, with pill count being a good tool to measure adherence and viral load assessment remaining the gold standard for assessing treatment success.
Suggested Reviewers:	Mary-Ann Davies Mary-Ann.Davies@uct.ac.za
	Anand Reddi areddi@fulbrightweb.org

CAPRISA
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Editors in Chief
Dr. Seth C. Kalichman, Ph.D
Center for HIV Prevention & Intervention
2006 Hillside Road, Unit 1248
University of Connecticut
Storrs, CT 06269

Email: aidsandbehavior@yahoo.com

2 November 2015

Dear Dr. Kalichman

Re: Original article for publication

We wish to submit an original article titled "**Assessing adherence to antiretroviral therapy in a rural paediatric cohort in KwaZulu-Natal, South Africa**" for review and publication.

This manuscript has not been published in this or a substantially similar form (in print or electronically, including on a web site), nor accepted for publication elsewhere, nor is it under consideration by another publication. All authors have read and approved the paper, and have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

Chanelle Smith (Corresponding Author)

Chanelle.smith@caprisa.org

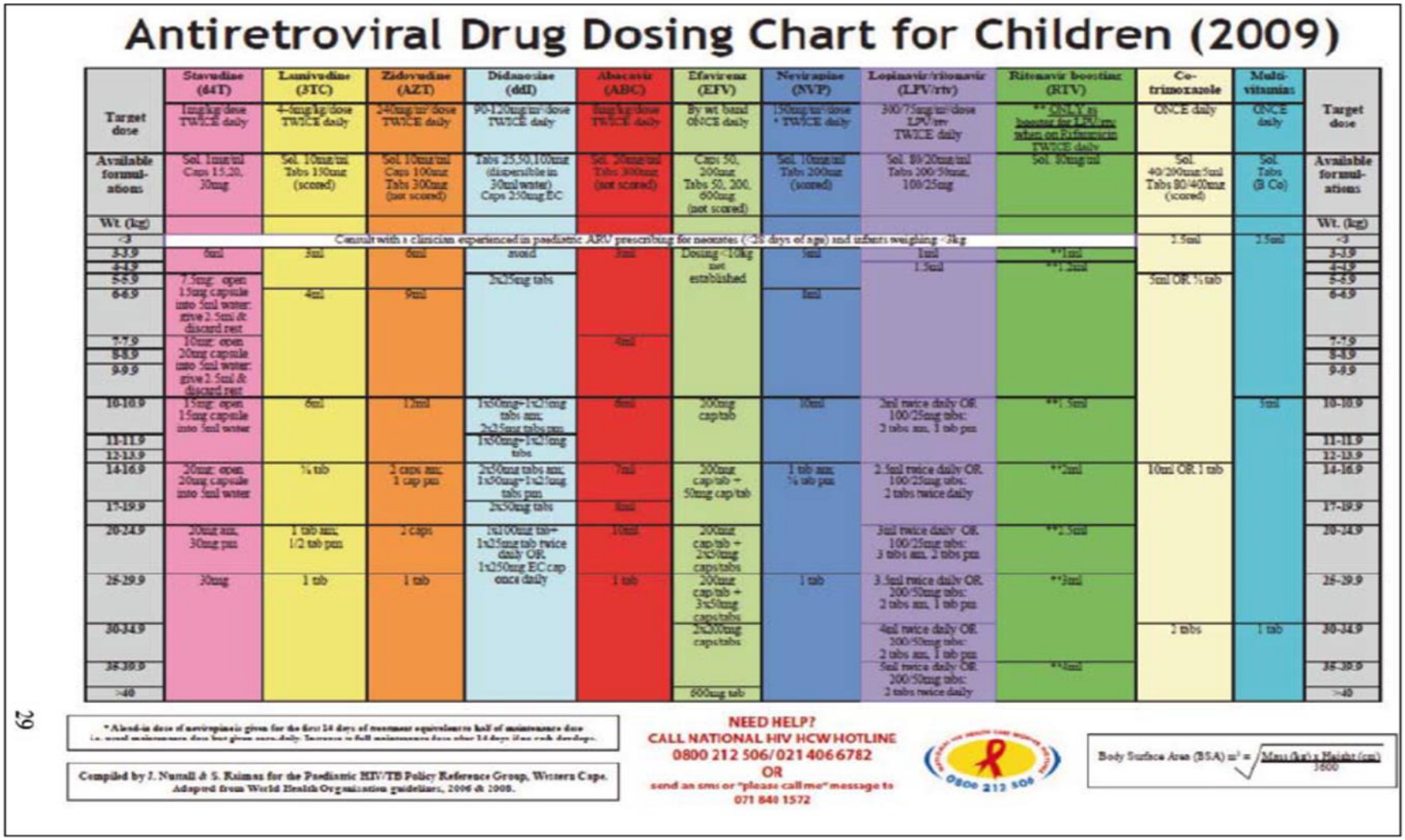
Tel: +27 33 260 6866

Appendix D: Paediatric Drug Dosing Guidelines 2008 – KwaZulu -Natal ARV Clinics

Weight (kg)	**D4T** Twice daily Suspension (1 mg/ml) or Capsules (20 mg)	**3TC** Twice daily Syrup (10 mg/ml) or Tablets (150 mg)		**EFAVIRENZ (Stocrin®)** Once daily Capsules (50 mg & 200 mg)	**KALETRA (LPV/RNV)** Twice daily Syrup (80/20 mg) or Capsules (133/33 mg)		**Intensive TB Treatment** (first 2 months) Mon - Fri, daily RHZ 60/30/150 Rimcure Paed 3FDC tablets	**Maintenance TB Treatment** (last 4 months) Mon - Fri, daily RH 60/30 Rifanah Sachets	**Additional RITONAVIR** (if on TB Rx) Twice daily Syrup (80mg/ml) or Capsules (100 mg)		**Bactrim** (PCP Prophylaxis) Daily Syrup, or Tablets	**Multivitamins** (Remember to give Vitamin A) Daily Vidaylin drops, Syrup, or Tablets
2 – 2,9	2,5 ml	1 ml			0,4 ml		½ tab	½ tab	0,3 ml		1,6 ml	0,6 ml Vidaylin
3 – 3,9	3,5 ml	1,4 ml			0,5 ml		½ tab	½ tab	0,4 ml		2 ml	0,6 ml Vidaylin
4 – 4,9	5 ml	1,8 ml			0,7 ml		½ tab	½ tab	0,5 ml		3 ml	0,6 ml Vidaylin
5 – 6,9	6 ml	2 ml			5-5,9 kg 1 ml 6-6,9 kg 1,5 ml		1 tab	1 tab	0,8 ml 1,2 ml		5 ml	2,5 ml syrup
7 – 9,9	10 ml	3 ml			7-7,9 kg 1,5 ml 8-9,9 kg 2 ml		1½ tabs	1½ tabs	1,2 ml 1,5 ml		5 ml	2,5 ml
10 – 11,9	10 ml	4 ml		200 mg	2 ml	1 caps	2 tabs	2 tabs	1,5 ml		7,5 ml	5 ml
12 – 14,9	15 ml	5 ml		200 mg	2 ml	am: 1 pm: 2	2 tabs	2 tabs	1,5 ml		7,5 ml	5 ml
15 – 16,9	15 ml	6 ml		200 mg + 50 mg	2 ml	am: 1 pm: 2	3 tabs	3 tabs	1,5 ml		10 ml	5 ml
17 – 19,9	20 mg	7 ml	½ tab	200 mg + 50 mg	2,5 ml	am: 1 pm: 2	3 tabs	3 tabs	2 ml	am: 1 pm: 2	10 ml or 1½ tabs	5 ml
20 – 24,9	20 mg	9 ml	am: ½ pm: 1	200 mg + 2 x 50 mg	3 ml	2 caps	4 tabs	4 tabs	2,5 ml	2 caps	15 ml or 2 tabs	1 tab
25 – 29,9	20 mg	11 ml	1 tab	200 mg + 3 x 50 mg	3,5 ml	2 caps	5 tabs	5 tabs	2,7 ml	2 caps	2 tabs	1 tab
30 – 34,9	20 mg	13 ml	1 tab	200 mg + 3 x 50 mg	4 ml	3 caps	6 tabs	6 tabs	3 ml	am: 2 pm: 3	2 tabs	1 tab
35 – 40	20 mg	15 ml	1 tab	200 mg + 200 mg	5 ml	3 caps	Use adult dose 2 Rifafour	Use adult dose 2 Rimactizid 150/75	3,8 ml	3 caps	2 tabs	1 tab

Compiled for KwaZulu-Natal ARV Clinics – Dr Kimesh Naidoo (Updated November 2008)

Appendix E: Paediatric Drug Dosing Guidelines 2009



Antiretroviral Drug Dosing Chart for Children (2009)

Target dose	Stavudine (d4T)	Lamivudine (3TC)	Zidovudine (AZT)	Didanosine (ddI)	Abacavir (ABC)	Efavirenz (EFV)	Nevirapine (NVP)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Co-trimoxazole	Multi-vitamins	Target dose
	1mg/kg dose TWICE daily	4-5mg/kg dose TWICE daily	240mg/m² dose TWICE daily	90-120mg/m² dose TWICE daily	8mg/kg dose TWICE daily	By wt band ONCE daily	150mg/m² dose * TWICE daily	300/75mg/m² dose LPV/rtv TWICE daily	** ONLY in booster for LPV/rtv when on Efavirenz TWICE daily	ONCE daily	ONCE daily	
Available formulations	Sol. 1mg/ml Caps 15,20, 30mg	Sol. 10mg/ml Tabs 150mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored)	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 20mg/ml Tabs 300mg (not scored)	Caps 50, 200mg Tabs 50, 200, 600mg (not scored)	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 80/20mg/ml Tabs 200/50mg, 100/25mg	Sol. 80mg/ml	Sol. 40/200mg/5ml Tabs 80/400mg (scored)	Sol. Tabs (B Co)	Available formulations
Wt. (kg)												Wt. (kg)
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg									2.5ml	2.5ml	<3
3-3.9	6ml	5ml	6ml	avoid	8ml	Dosing <10kg not established	5ml	1ml	**1ml			3-3.9
4-4.9								1.5ml	**1.5ml			4-4.9
5-5.9	7.5mg: open 15mg capsule into 5ml water: give 2.5ml & discard rest			2x25mg tabs						5ml OR ½ tab		5-5.9
6-6.9		4ml	9ml				8ml					6-6.9
7-7.9	10mg: open 20mg capsule into 5ml water: give 2.5ml & discard rest				4ml							7-7.9
8-8.9												8-8.9
9-9.9												9-9.9
10-10.9	15mg: open 15mg capsule into 5ml water	6ml	12ml	1x50mg+1x25mg tabs am; 2x25mg tabs pm	6ml	200mg cap/tab	10ml	2ml twice daily OR 100/25mg tabs: 2 tabs am, 1 tab pm	**1.5ml		5ml	10-10.9
11-11.9				1x50mg+1x25mg tabs								11-11.9
12-13.9												12-13.9
14-16.9	20mg: open 20mg capsule into 5ml water	¼ tab	2 caps am; 1 cap pm	2x50mg tabs am; 1x50mg+1x25mg tabs pm	7ml	200mg cap/tab + 50mg cap/tab	1 tab am; ¼ tab pm	2.5ml twice daily OR 100/25mg tabs: 2 tabs twice daily	**2ml	10ml OR 1 tab		14-16.9
17-19.9				2x50mg tabs	8ml							17-19.9
20-24.9	20mg am, 30mg pm	1 tab am, 1/2 tab pm	2 caps	1x100mg tab+ 1x25mg tab twice daily OR 1x250mg EC cap once daily	10ml	200mg cap/tab + 2x50mg caps/tabs		3ml twice daily OR 100/25mg tabs: 3 tabs am, 2 tabs pm	**2.5ml			20-24.9
25-29.9	30mg	1 tab	1 tab		1 tab	200mg cap/tab + 3x50mg caps/tabs	1 tab	3.5ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm	**3ml			25-29.9
30-34.9						2x200mg caps/tabs		4ml twice daily OR 200/50mg tabs: 2 tabs am, 1 tab pm		2 tabs	1 tab	30-34.9
35-39.9								5ml twice daily OR 200/50mg tabs: 2 tabs twice daily	**4ml			35-39.9
>40						600mg tab						>40

* Ramp-in dose of nevirapine is given for the first 14 days of treatment: equivalent to half of maintenance dose i.e. usual maintenance dose but given once daily. Increase to full maintenance dose after 14 days if no rash develops.

Compiled by J. Nuttall & S. Raimas for the Paediatric HIV/TB Policy Reference Group, Western Cape. Adapted from World Health Organisation guidelines, 2006 & 2008.

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0800 212 506/021 406 6782
OR
send an sms or "please call me" message to
071 840 1572

0800 212 506

Body Surface Area (BSA) $m^2 = \sqrt{\frac{\text{Mass (kg)} \times \text{Height (cm)}}{3600}}$

29

Appendix F: Paediatric Drug Dosing Guidelines 2010

SIMPLIFIED PAEDIATRIC DRUG DOSING FOR RESOURCE POOR SETTINGS: First Line

Weight (kg)	ABACAVIR 8 mg/kg/dose twice daily Syrup 20 mg/ml Tablets 300 mg	D4T 1 mg/kg/dose twice daily Suspension 1 mg/ml Capsules 15, 20, 30 mg	3TC 4 mg/kg/dose twice daily Syrup 10 mg/ml Tablets 150 mg	EFAVIRENZ Once daily Capsules 50, 200 mg Tablets 50, 200, 600 mg	LPV/r (Kaletra®/Aluvia®) 300/75 mg/m²/dose twice daily Syrup (Kaletra®) 80/20 mg/ml Tablets (Aluvia®) 200/50 mg		ADDITIONAL RITONAVIR Added to LPV/r while on Rifampicin twice daily Syrup 80 mg/ml	Bactrim (PCP Prophylaxis) Daily Syrup 40/200 mg/5ml Tablets 80/400 mg		Multivitamins Daily Syrup, or Tablets
< 3	CONSULT LOCAL REFERRAL CENTRE							2.5 ml		2.5 ml
3 – 3.9	3 ml	6 ml	3 ml		1 ml		1 ml	2.5 ml		2.5 ml
4 – 4.9	3 ml	6 ml	3 ml		1.5 ml		1.2 ml	2.5 ml		2.5 ml
5 – 5.9	3 ml	7.5 ml	3 ml		1.5 ml		1.2 ml	5 ml	½ tab	2.5 ml
6 – 6.9	3 ml	7.5 ml	4 ml		1.5 ml		1.2 ml	5 ml	½ tab	2.5 ml
7 – 7.9	4 ml	10 ml	4 ml		1.5 ml		1.2 ml	5 ml	½ tab	2.5 ml
8 – 8.9	4 ml	10 ml	4 ml		1.5 ml		1.2 ml	5 ml	½ tab	2.5 ml
9 – 9.9	4 ml	10 ml	4 ml		1.5 ml		1.2 ml	5 ml	½ tab	2.5 ml
10 – 10.9	6 ml	15 ml	6 ml	200 mg	2 ml		1.5 ml	5 ml	½ tab	5 ml
11 – 11.9	6 ml	15 ml	6 ml	200 mg	2 ml		1.5 ml	5 ml	½ tab	5 ml
12 – 13.9	6 ml	15 ml	6 ml	200 mg	2 ml		1.5 ml	5 ml	½ tab	5 ml
14 – 16.9	7 ml **or** ½ tab	20 mg	½ tablet	200 mg + 50 mg	2.5 ml		2 ml	10 ml	1 tab	5 ml
17 – 19.9	8 ml **or** ½ tab	20 mg	½ tablet	200 mg + 50 mg	2.5 ml		2 ml	10 ml	1 tab	5 ml
20 – 24.9	10 ml **or** ½ tab	20 mg am 30 mg pm	1 tablet am ½ tablet pm	200 mg + 2 x 50 mg	3 ml		2.5 ml	10 ml	1 tab	5 ml
25 – 29.9	1 tablet	30 mg	1 tablet	200 mg + 3 x 50 mg	3.5 ml	2 tab am 1 tab pm	3 ml	10 ml	1 tab	5 ml
30 – 34.9	1 tablet	30 mg	1 tablet	2 x 200 mg	4 ml	2 tab am 1 tab pm	3 ml	2 tablets		1 tablet
35 – 39.9	1 tablet	30 mg	1 tablet	2 x 200 mg	5 ml	2 tab	4 ml	2 tablets		1 tablet
> 40	1 tablet	30 mg	1 tablet	600 mg	5 ml	2 tab	4 ml	2 tablets		1 tablet

Appendix G: Paediatric Drug Dosing Guidelines 2011

Antiretroviral Drug Dosing Chart for Children (2011)

Target dose	Stavudine (d4T)	Lamivudine (3TC)	Zidovudine (AZT)	Didanosine (ddI)	Abacavir (ABC)	Efavirenz (EFV)	Nevirapine (NVP)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Co-trimoxazole	Multi-vitamins	Target dose
	1mg/kg/dose TWICE daily	4-6mg/kg/dose TWICE daily	240mg/m²/dose TWICE daily	90-120mg/m²/dose TWICE daily	8mg/kg/dose TWICE daily	8y wt. band ONCE daily	150mg/m²/dose TWICE daily (after once daily lead-in)	300/75mg/m²/dose LPV/rtv TWICE daily	** ONLY as booster for LPV/rtv when on Rifampicin TWICE daily	ONCE daily	ONCE daily	
Available formulations	Sol. 1mg/ml Caps 15,20, 30mg	Sol. 10mg/ml Tabs 150mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored)	Tabs 25,50,100mg (dispersible in at least 30ml water) Caps 250mg EC	Sol. 20mg/ml Tabs 300mg (not scored)	Caps 50, 200mg Tabs 50, 200, 600mg (not scored)	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 80/20mg/ml * Tabs 200/50mg, 100/25mg	Sol. 80mg/ml	Sol. 40/200mg/5ml Tabs 80/400mg (scored)	Sol. Tabs (B Co)	Available formulations
Wt. (kg)												Wt. (kg)
<3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg									2.5ml	2.5ml	<3
3-3.9	6ml	3ml	6ml	avoid	2ml	Dosing <10kg not established	5ml	1ml	**5ml			3-3.9
4-4.9								1.5ml	**1.2ml			4-4.9
5-5.9	7.5mg: open 15mg capsule into 5ml water: give 2.5ml & discard rest			2x25mg tabs (am & pm)						5ml OR ½ tab		5-5.9
6-6.9		4ml	9ml	1x50mg+1x25mg tabs am; 2x25mg tabs pm	4ml		6ml					6-6.9
7-7.9	10mg: open 20mg capsule into 5ml water: give 2.5ml & discard rest		1 cap									7-7.9
8-8.9												8-8.9
9-9.9												9-9.9
10-10.9	15mg: open 15mg capsule into 5ml water	6ml		1x50mg+1x25mg tabs (am & pm)	5ml	200mg cap/tab	10ml	2ml twice daily OR 100/25mg tabs: 2 tabs am, 1 tab pm	**1.5ml		5ml	10-10.9
11-11.9												11-11.9
12-13.9												12-13.9
14-16.9	20mg: open 20mg capsule into 5ml water (if child unable to swallow capsule)	¾ tab	2 caps am; 1 cap pm	2x50mg tabs am; 1x50mg+1x25mg tabs pm	6ml	200mg cap/tab + 2x50mg cap/tab	1 tab am; ¾ tab pm	2.5ml twice daily OR 100/25mg tabs: 2 tabs twice daily	**2ml	10ml OR 1 tab		14-16.9
17-19.9												17-19.9
20-24.9		1 tab am; ¾ tab pm	2 caps	2x50mg tabs (am & pm)	10ml			3ml twice daily OR 100/25mg tabs: 2 tabs twice daily	**2.5ml			20-24.9
25-29.9	30mg	1 tab	1 tab	1x100mg tab+ 1x25mg tab twice daily OR 1x250mg EC cap once daily	1 tab	2x200mg caps/tabs	1 tab	3.5ml twice daily OR 100/25mg tabs: 3 tabs twice daily	**3ml			25-29.9
30-34.9								4ml twice daily OR 100/25mg tabs: 3 tabs twice daily		2 tabs	1 tab	30-34.9
35-39.9						600mg tab		5ml twice daily OR 200/50mg tabs: 2 tabs twice daily	**4ml			35-39.9
>40												>40

*Children 14-24.9 kg may also be dosed with LPV/rtv 200/50 mg tabs as follows: 1 tab twice daily
Children 25-34.9 kg may also be dosed with LPV/rtv 200/50 mg tabs as follows: 2 tabs am; 1 tab pm

Body Surface Area (BSA) $m^2 = \sqrt{\frac{\text{Mass (kg)} \times \text{Height (cm)}}{3600}}$

Compiled by J. Nuttall & S. Raiman for the Paediatric HIV/TB Policy Reference Group, Western Cape.
Adapted from World Health Organisation guidelines, 2010.

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Appendix H: Paediatric Drug Dosing Guidelines 2012

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ANTIRETROVIRAL DRUG DOSING CHART FOR CHILDREN 2012

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health

	Abacavir (ABC)		Lamivudine (3TC)		Efavirenz (EFV)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Stavudine (d4T)	Didanosine (ddI)	Nevirapine (NVP)	Zidovudine (AZT)	
Target Dose	8mg/kg TWICE daily OR ≥10kg: 16mg/kg ONCE daily		4mg/kg TWICE daily OR ≥10kg: 8mg/kg ONCE daily		By weight band ONCE daily	300/75mg/m²/dose LPV/rtv TWICE daily	ONLY as booster for LPV/rtv when on Rifampicin TWICE daily (0.75xLPV dose bd)	1mg/kg/dose TWICE daily	180-240mg/m²/dose ONCE daily	160-200 mg/m²/dose TWICE daily (after once daily lead-in x 2 wks)	180-240mg/m²/dose TWICE daily	**Target Dose**
Available Formulations	Sol 20mg/ml Tabs 300mg (not scored)		Sol. 10mg/ml Tabs 150mg (scored) 300mg		Caps 50,200mg Tabs 50, 200, 600mg (not scored)	Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg	Sol. 80mg/ml	Sol. 1mg/ml Caps 15, 20, 30mg	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored)	**Available Formulations**
Wt. (kg)	**Currently available tablet formulations of abacavir, efavirenz, LPV/rtv and AZT are film-coated and must be swallowed whole and NOT chewed, divided or crushed**											**Wt. (kg)**
<3	**Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg**											**<3**
3-3.9	2ml bd		2ml bd		Avoid using when <10kg or <3 years: dosing not established	*1ml bd	1ml bd	6ml	Avoid	5ml bd	6ml bd	**3-3.9**
4-4.9												**4-4.9**
5-5.9	3ml bd		3ml bd			*1.5ml bd	1.5ml bd	7.5mg bd: open 15mg capsule into 5ml water: give 2.5ml	100mg od: (2x50mg tabs)			**5-5.9**
6-6.9									125mg od: (1x100mg + 1x25mg tabs)	8ml bd	9ml bd	**6-6.9**
7-7.9	4ml bd		4ml bd					10mg bd: open 20mg capsule into 5ml water: give 2.5ml				**7-7.9**
8-8.9											1 cap bd OR 12ml bd	**8-8.9**
9-9.9												**9-9.9**
10-10.9	Choose only one option:		Choose only one option:		200mg nocte (1x200mg cap/tab)	2ml bd	1.5ml bd	15mg bd: open 15mg capsule into 5ml water	150mg od: (1x100mg + 1x50mg tabs)	10ml bd		**10-10.9**
11-13.9	6ml bd	12ml od	6ml bd	12ml od								**11-13.9**
14-16.9	8ml bd	1 tab od OR 15ml od	1/2x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od	300mg nocte: (200mg cap/tab + 2x50mg cap/tab)	Choose one option: -2.5ml bd -100/25mg paeds tabs: 2 bd -200/50mg adult tabs: 1 bd	2ml bd	20mg bd: open 20mg capsule into 5ml water (if the child is unable to swallow a capsule)	175mg od: (1x100mg + 1x50mg + 1x25mg)	1 tab am 1/2 tab pm OR 15ml bd	2 caps am 1 cap pm OR 15ml bd	**14-16.9**
17-19.9												**17-19.9**
20-24.9	10ml bd	20ml od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 30ml od		Choose one option: -3ml bd - 100/25mg paeds tabs: 2 bd - 200/50mg adult tabs: 1 bd	2.5ml bd		200mg od: (2 x 100mg tabs)		2 caps bd OR 20ml bd	**20-24.9**
25-29.9	1x300mg tab bd	2x300mg tabs od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od	400mg nocte: (2x200mg caps/tabs)	Choose one option: - 3.5ml bd - 100/25mg paeds tabs: 3 bd - #200/50mg adult tabs: 1 bd + 100/25mg paeds tabs 1 bd	3ml bd	30mg bd	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1 tab bd	**25-29.9**
30-34.9						Choose one option: - 4ml bd - 100/25mg paeds tabs: 3 bd - #200/50mg adult tabs: 1 bd + 100/25mg paeds tabs 1 bd						**30-34.9**
35-39.9						Choose one option: - 5ml bd - 200/50mg adult tabs: 2 bd	4ml bd					**35-39.9**
>40					600mg tab nocte							**>40**

od = once a day
bd = twice a day

* Avoid PLV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception) or obtain expert advice.
# Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm

Weight (kg)	3-4.9	5-9.9	10-13.9	14-29.9	≥30
Cotrimoxazole Dose	2.5ml od	5ml od	5ml od	10ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5ml od	2.5ml od	5ml od	5ml od	10ml or 1 tab od

Appendix I: Paediatric Drug Dosing Guidelines 2013

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REPUBLIC OF SOUTH AFRICA

ANTIRETROVIRAL DRUG DOSING CHART FOR CHILDREN 2013

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians Society in collaboration with the Department of Health

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

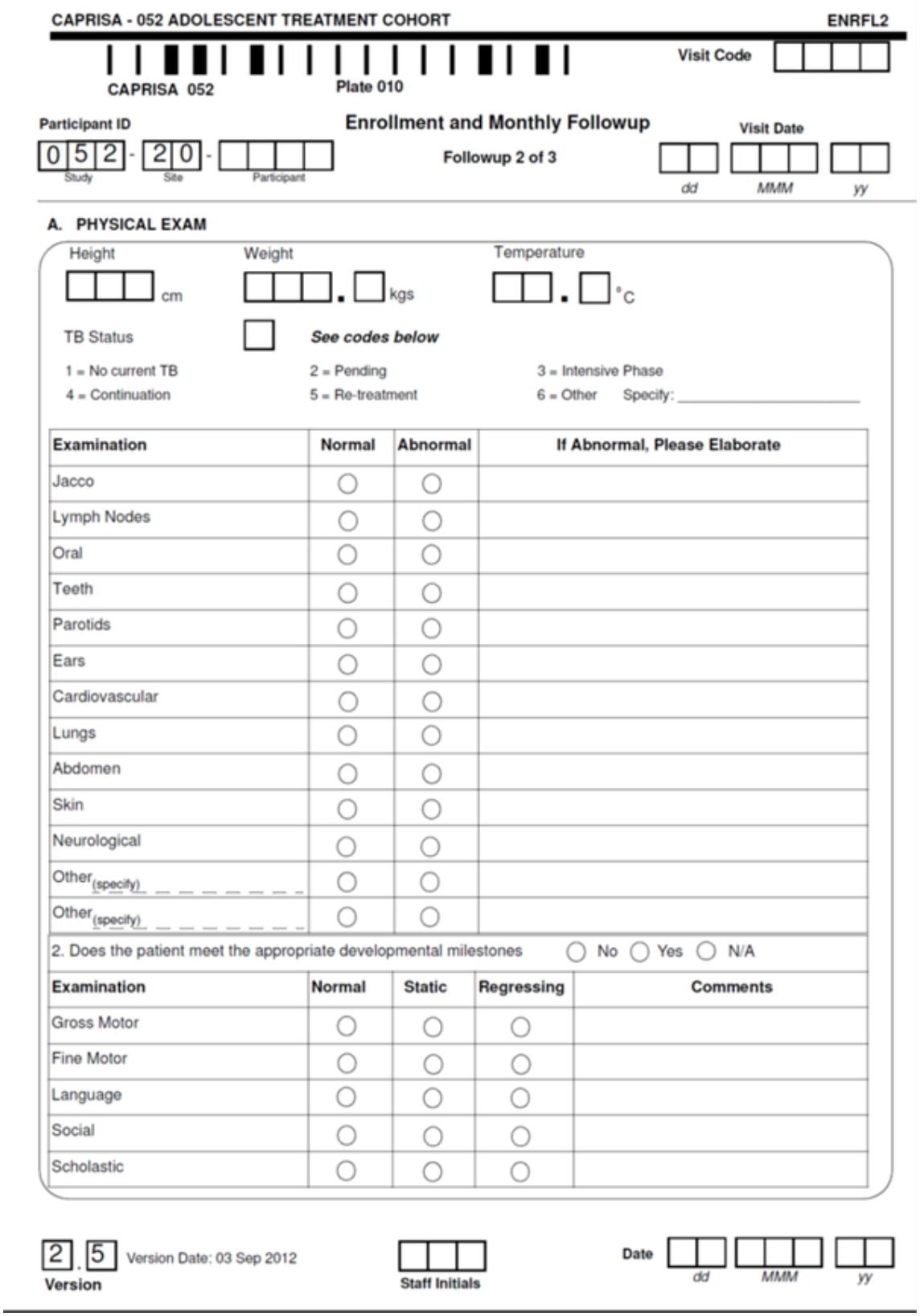
	Abacavir (ABC)		Lamivudine (3TC)		Efavirenz (EFV)	Lopinavir/ritonavir (LPV/rtv)	Ritonavir boosting (RTV)	Stavudine (d4T)	Didanosine (ddI)	Nevirapine (NVP)	Zidovudine (AZT)	
Target Dose	8mg/kg TWICE daily **OR** **≥10kg:** 16mg/kg ONCE daily		4mg/kg TWICE daily **OR** **≥10kg:** 8mg/kg ONCE daily		By weight band **ONCE** daily	300/75mg/m²/dose LPV/rtv **TWICE** daily	ONLY as booster for LPV/rtv when on Rifampicin: **TWICE** daily (0.75xLPV dose bd)	1mg/kg/dose **TWICE** daily	180-240mg/m²/dose **ONCE** daily	160-200 mg/m²/dose **TWICE** daily (after once daily lead-in x 2 wks)	180-240mg/m²/dose **TWICE** daily	**Target Dose**
Available Formulations	Sol 20mg/ml Tabs 60mg (scored dispersible), 300mg (not scored), ABC/3TC 600/300mg		Sol. 10mg/ml Tabs 150mg (scored), 300mg, ABC/3TC 600/300mg		Caps 50,200mg Tabs 50,200, 600mg (not scored)	Sol. 80/20mg/ml Adult Tabs 200/50mg, Paeds Tabs 100/25mg	Sol. 80mg/ml	Sol. 1mg/ml Caps 15,20,30mg	Tabs 25,50,100mg (dispersible in 30ml water) Caps 250mg EC	Sol. 10mg/ml Tabs 200mg (scored)	Sol. 10mg/ml Caps 100mg Tabs 300mg (not scored), AZT/3TC 300/150mg	**Available Formulations**
Wt. (kg)	**Currently available tablet formulations of abacavir (except 60mg), efavirenz, LPV/rtv and AZT must be swallowed whole and NOT chewed, divided or crushed**											**Wt. (kg)**
<3	**Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing <3kg**											**<3**
3-3.9	2ml bd		2ml bd		**Avoid using when <10kg or <3 years:** dosing not established	*1ml bd	1ml bd	6ml	Avoid	5ml bd	6ml bd	**3-3.9**
4-4.9								**7.5mg bd:** open 15mg capsule into 5ml water: give 2.5ml	100mg od: (2x50mg tabs)			**4-4.9**
5-5.9	3ml bd		3ml bd			*1.5ml bd	1.5ml bd					**5-5.9**
6-6.9									125mg od: (1x100mg + 1x25mg tabs)	8ml bd	9ml bd	**6-6.9**
7-7.9	4ml bd		4ml bd					**10mg bd:** open 20mg capsule into 5ml water: give 2.5ml				**7-7.9**
8-8.9											1 cap bd OR 12ml bd	**8-8.9**
9-9.9												**9-9.9**
10-10.9	Choose only one option: 6ml bd OR 2x60mg tabs bd	Choose only one option: 12ml od OR 4x60mg tabs od	Choose only one option: 6ml bd	12ml od	200mg nocte (1x200mg cap/tab)	2ml bd	1.5ml bd	**15mg bd:** open 15mg capsule into 5ml water	150mg od: (1x100mg + 1x50mg tabs)	10ml bd		**10-10.9**
11-13.9												**11-13.9**
14-16.9	8ml bd OR 2.5x60mg tabs bd	5x60mg tabs od OR 1x300mg tab od OR 15ml od	½ x150mg tab bd OR 8ml bd	1x150mg tab od OR 15ml od	300mg nocte: (200mg cap/tab + 2x50mg cap/tab)	Choose one option: -2.5ml bd -100/25mg **paeds tabs:** 2 bd -200/50mg **adult tabs:** 1 bd	2ml bd	**20mg bd:** open 20mg capsule into 5ml water (if the child is unable to swallow a capsule)	175mg od: (1x100mg + 1x50mg + 1x25mg)	1 tab am ½ tab pm OR 15ml bd	2 caps am 1 cap pm OR 15ml bd	**14-16.9**
17-19.9												**17-19.9**
20-22.9	10ml bd OR 3x60mg tabs bd	1x300mg tab + 1x60mg tab od	1x150mg tab bd OR 15ml bd	2x150mg tab od OR 1x300mg tab od OR 20ml od		Choose one option: -3ml bd - 100/25mg **paeds tabs:** 2 bd - 200/50mg **adult tabs:** 1 bd	2.5ml bd		200mg od: (2x100mg tabs)		2 caps bd OR 20ml bd	**20-22.9**
23-24.9		1x300mg tab + 2x60mg tabs od										**23-24.9**
25-29.9	1x300mg tab bd	2x300mg tabs od OR 1xABC/3TC 600/300mg tab od	1x150mg tab bd	2x150mg tabs od OR 1x300mg tab od OR 1xABC/3TC 600/300mg tab od	400mg nocte: (2x200mg caps/ tabs)	Choose one option: - 2.5ml bd - 100/25mg **paeds tabs:** 3 bd - **≠**200/50mg **adult tabs:** 1 bd + 100/25mg **paeds tabs:** 1 bd	3ml bd	**30mg bd**	250mg od: (2x100mg + 1x50mg tab) OR 1x250mg EC cap od	1 tab bd	1x300mg tab bd OR 1xAZT/3TC 300/150mg tab bd	**25-29.9**
30-34.9						Choose one option: - 4ml bd - 100/25mg **paeds tabs:** 3 bd - **≠**200/50mg **adult tabs:** 1 bd + 100/25mg **paeds tabs:** 1 bd						**30-34.9**
35-39.9						Choose one option: - 5ml bd - 200/50mg **adult tabs:** 2 bd	4ml bd					**35-39.9**
>40					600mg tab nocte							**>40**

od = once a day (usually at night)
bd = twice a day

* Avoid LPV/rtv solution in any full term infant <14 days of age and any premature infant <14 days after their due date of delivery (40 weeks post conception); or obtain expert advice.
# Children 25-34.9kg may also be dosed with LPV/rtv 200/50mg adult tabs: 2 tabs am; 1 tab pm

Weight (kg)	3-4.9	5-9.9	10-13.9	14-29.9	≥30
Cotrimoxazole Dose	2.5ml od	5ml od	5ml od	10ml or 1 tab od	2 tabs od
Multivitamin Dose	2.5ml od	2.5ml od	5ml od	5ml od	10ml or 1 tab od

Appendix J: Plate #010 – Enrolment and Monthly Follow-up



CAPRISA - 052 ADOLESCENT TREATMENT COHORT ENRFL2

CAPRISA 052 Plate 010 Visit Code

Participant ID: 052 - 20 - (Study - Site - Participant)

Enrollment and Monthly Followup

Followup 2 of 3

Visit Date: dd MMM yy

A. PHYSICAL EXAM

Height ___ cm Weight ___.__ kgs Temperature ___.__ °C

TB Status ___ See codes below

1 = No current TB 2 = Pending 3 = Intensive Phase

4 = Continuation 5 = Re-treatment 6 = Other Specify: _____

Examination	Normal	Abnormal	If Abnormal, Please Elaborate
Jacco	○	○	
Lymph Nodes	○	○	
Oral	○	○	
Teeth	○	○	
Parotids	○	○	
Ears	○	○	
Cardiovascular	○	○	
Lungs	○	○	
Abdomen	○	○	
Skin	○	○	
Neurological	○	○	
Other (specify) _____	○	○	
Other (specify) _____	○	○	

2. Does the patient meet the appropriate developmental milestones ○ No ○ Yes ○ N/A

Examination	Normal	Static	Regressing	Comments
Gross Motor	○	○	○	
Fine Motor	○	○	○	
Language	○	○	○	
Social	○	○	○	
Scholastic	○	○	○	

2.5 Version Version Date: 03 Sep 2012 Staff Initials Date: dd MMM yy

Appendix K: Plate #011 – Enrolment and Monthly Follow-up

CAPRISA - 052 ADOLESCENT TREATMENT COHORT — ENRFL3

CAPRISA 052 — Plate 011 — Visit Code

Participant ID: 052 - 20 - (Study - Site - Participant)

Enrollment and Monthly Followup

Followup 3 of 3

B. TOXICITY AND MONITORING/ADVERSE EVENTS

(Exclude intercurrent and non-ARV drug related cause of symptom)

Complaint/Symptom	Observation	Complaint/Symptom	Observation
Fatigue	○ No ○ Yes	Sleep disruption	○ No ○ Yes
Headache	○ No ○ Yes	Anorexia	○ No ○ Yes
Vomitting	○ No ○ Yes	Diarrhoea	○ No ○ Yes
Abdominal pain	○ No ○ Yes	Painful feet	○ No ○ Yes
Fever	○ No ○ Yes	Other (specify) _____	○ No ○ Yes
Rash	○ No ○ Yes	Other (specify) _____	○ No ○ Yes

D. ART REGIMEN

Change ○ No ○ Yes → If ART commenced/changed:

Start Date: dd MMM yy

Stop Date: dd MMM yy

Regimen: ARV 1 | ARV 2 | ARV 3 — ***See codes below***

1= Efavirenz = EFV; 2= Lamivudine = 3TC; 3= Stavudine = D_4T; 4= Nevirapine = NVP; 5= Didanosine = ddI; 7 = Zidovudine = AZT; 9= Abacavir = ABC; 11 = Tenofovir = TDF; 13= Kaletra

Reason for Modification — ***See codes below***

1 - Initial dose
2 - Completed treatment
3 - Laboratory/clinical toxicity
4 - Requires prohibited medication
5 Nevirapine lead in
6 - Weight change
7 - Toxicity decreased
8 - Clinician request
9 - Participant request
10 - Treatment failure
11 - Intolerance
12 - Concomitant conditions
13 - Creatinine clearance value
14 - Stopped rifampicin
15 - Other, specify _____

Patient to come back after: ____ **weeks**

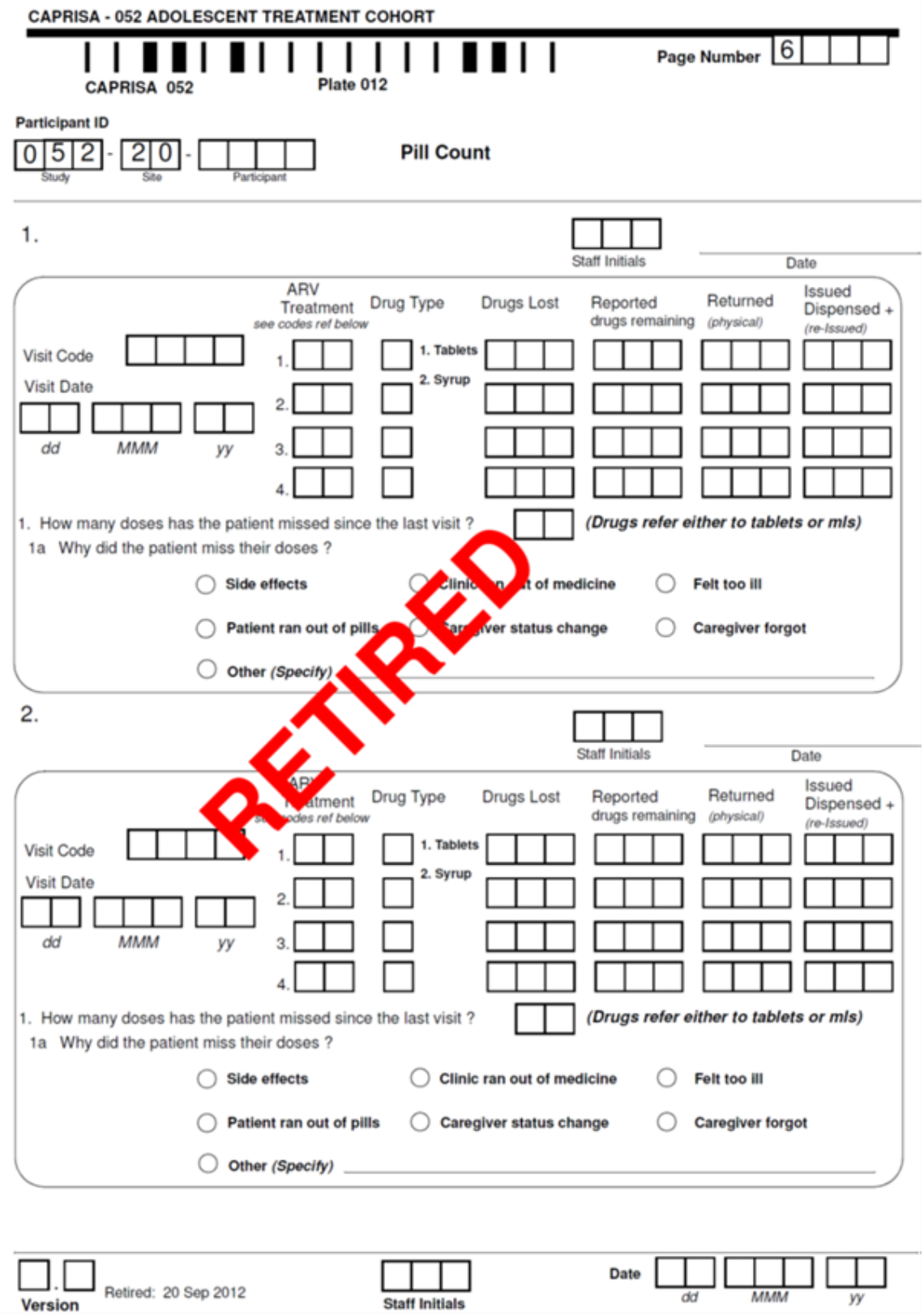
Comments _____

2.5 Version — Version Date: 03 Sep 2012

Staff Initials

Date: dd MMM yy

Appendix L: Plate #012 – Pill count



CAPRISA - 052 ADOLESCENT TREATMENT COHORT

CAPRISA 052 Plate 012 Page Number 6

Participant ID: 052 - 20 - ____ (Study - Site - Participant)

Pill Count

1. Staff Initials ____ Date ____

Visit Code / Visit Date (dd MMM yy)	ARV Treatment (see codes ref below)	Drug Type (1. Tablets, 2. Syrup)	Drugs Lost	Reported drugs remaining	Returned (physical)	Issued Dispensed + (re-Issued)
	1.					
	2.					
	3.					
	4.					

1. How many doses has the patient missed since the last visit ? ____ *(Drugs refer either to tablets or mls)*

1a Why did the patient miss their doses ?

- ○ Side effects
- ○ Clinic ran out of medicine
- ○ Felt too ill
- ○ Patient ran out of pills
- ○ Caregiver status change
- ○ Caregiver forgot
- ○ Other *(Specify)* ____

RETIRED

2. Staff Initials ____ Date ____

Visit Code / Visit Date (dd MMM yy)	ARV Treatment (see codes ref below)	Drug Type (1. Tablets, 2. Syrup)	Drugs Lost	Reported drugs remaining	Returned (physical)	Issued Dispensed + (re-Issued)
	1.					
	2.					
	3.					
	4.					

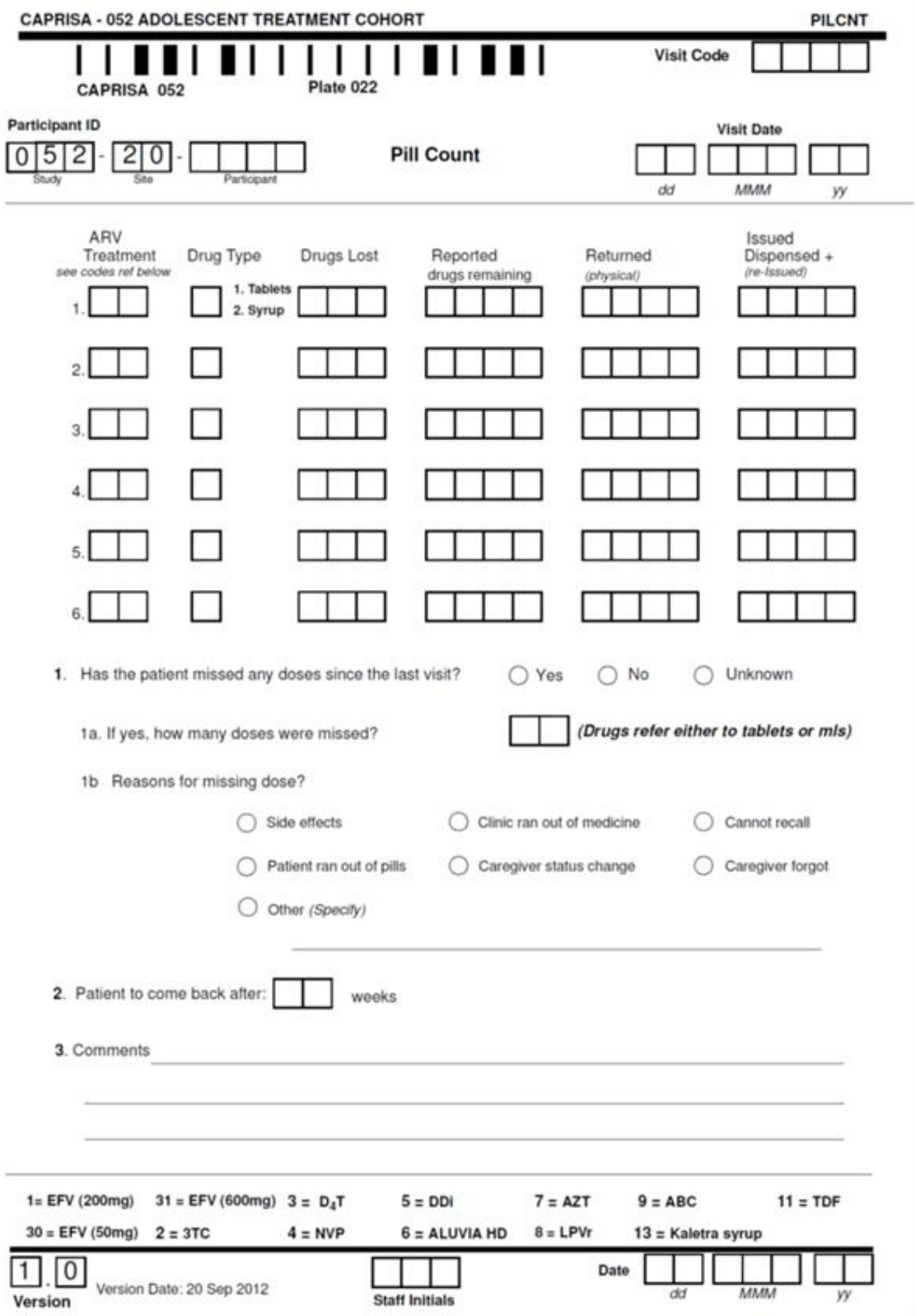
1. How many doses has the patient missed since the last visit ? ____ *(Drugs refer either to tablets or mls)*

1a Why did the patient miss their doses ?

- ○ Side effects
- ○ Clinic ran out of medicine
- ○ Felt too ill
- ○ Patient ran out of pills
- ○ Caregiver status change
- ○ Caregiver forgot
- ○ Other *(Specify)* ____

Version ____.____ Retired: 20 Sep 2012 Staff Initials ____ Date ____ (dd MMM yy)

Appendix M: Plate #022 – Pill count



CAPRISA - 052 ADOLESCENT TREATMENT COHORT

PILCNT

CAPRISA 052

Plate 022

Visit Code

Participant ID

0 5 2 - 2 0 - ____

Study | Site | Participant

Pill Count

Visit Date

dd | MMM | yy

	ARV Treatment (see codes ref below)	Drug Type (1. Tablets 2. Syrup)	Drugs Lost	Reported drugs remaining	Returned (physical)	Issued Dispensed + (re-Issued)
1.						
2.						
3.						
4.						
5.						
6.						

1. Has the patient missed any doses since the last visit? ○ Yes ○ No ○ Unknown

1a. If yes, how many doses were missed? ____ *(Drugs refer either to tablets or mls)*

1b Reasons for missing dose?

○ Side effects ○ Clinic ran out of medicine ○ Cannot recall

○ Patient ran out of pills ○ Caregiver status change ○ Caregiver forgot

○ Other *(Specify)* _____

2. Patient to come back after: ____ weeks

3. Comments _____

1= EFV (200mg) 31 = EFV (600mg) 3 = D_4T 5 = DDi 7 = AZT 9 = ABC 11 = TDF

30 = EFV (50mg) 2 = 3TC 4 = NVP 6 = ALUVIA HD 8 = LPVr 13 = Kaletra syrup

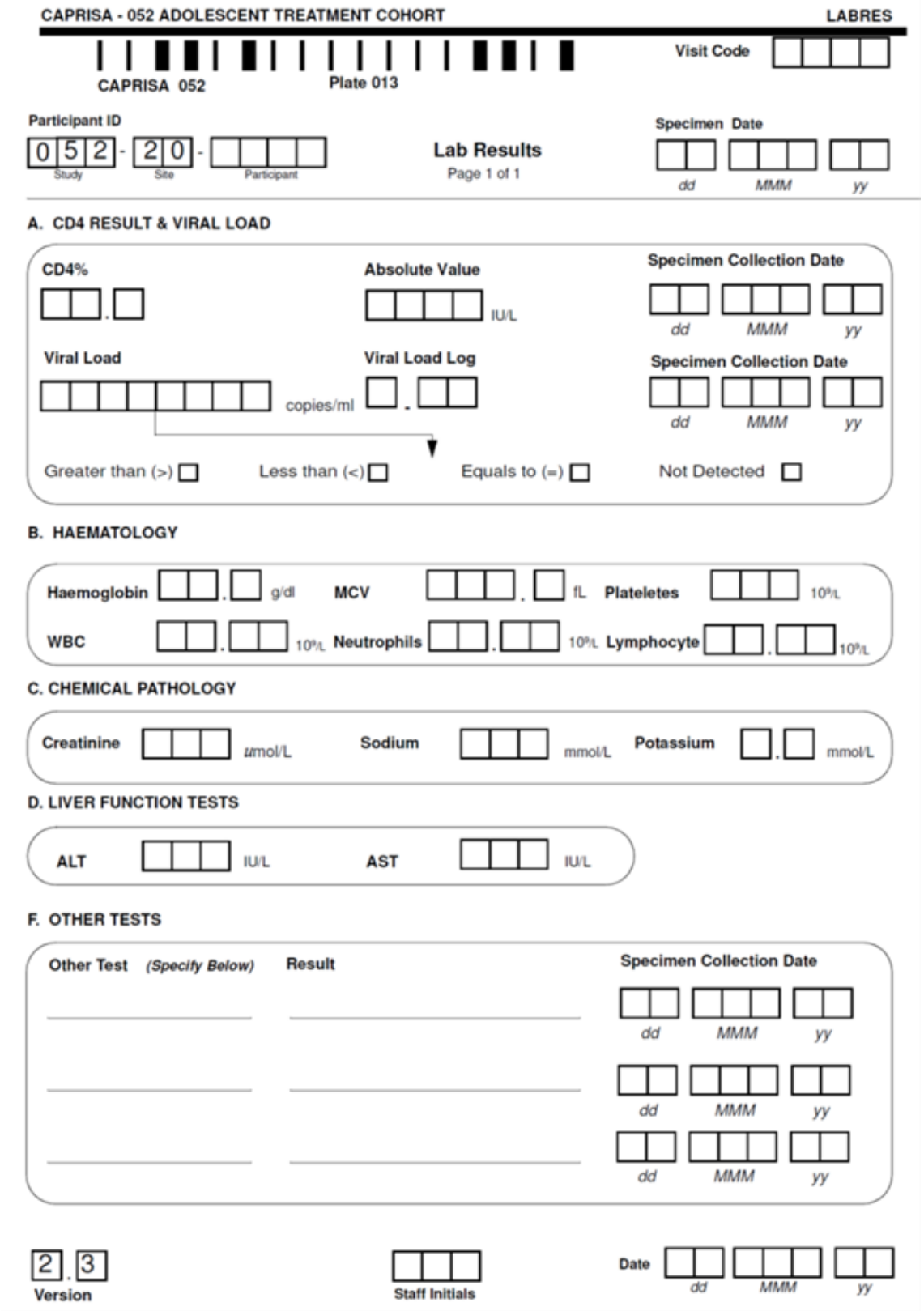
1.0 Version

Version Date: 20 Sep 2012

Staff Initials

Date dd | MMM | yy

Appendix N: Plate #013 – Lab Results



CAPRISA - 052 ADOLESCENT TREATMENT COHORT

LABRES

CAPRISA 052

Plate 013

Visit Code

Participant ID

0 5 2 - 2 0 - ____

Study Site Participant

Lab Results

Page 1 of 1

Specimen Date

dd MMM yy

A. CD4 RESULT & VIRAL LOAD

CD4% ___.___

Absolute Value ____ IU/L

Specimen Collection Date

dd MMM yy

Viral Load ____ copies/ml

Viral Load Log ___.___

Specimen Collection Date

dd MMM yy

Greater than (>) ☐ Less than (<) ☐ Equals to (=) ☐ Not Detected ☐

B. HAEMATOLOGY

Haemoglobin ___.___ g/dl MCV ___.___ fL Plateletes ___ 10^9/L

WBC ___.___ 10^9/L Neutrophils ___.___ 10^9/L Lymphocyte ___.___ 10^9/L

C. CHEMICAL PATHOLOGY

Creatinine ___ µmol/L Sodium ___ mmol/L Potassium ___.___ mmol/L

D. LIVER FUNCTION TESTS

ALT ___ IU/L AST ___ IU/L

F. OTHER TESTS

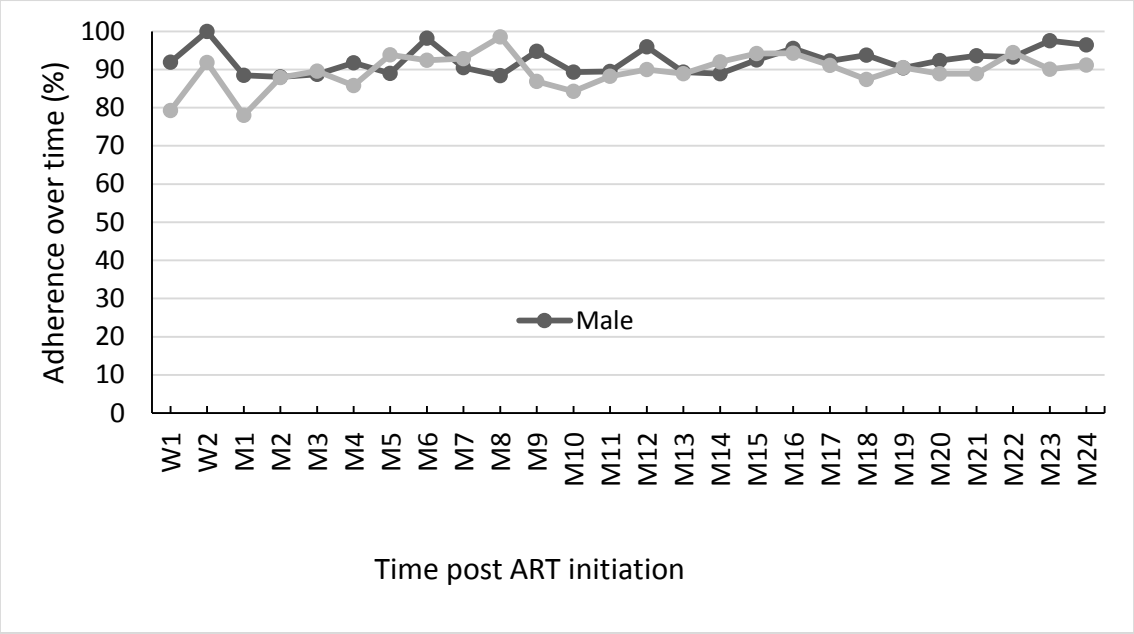
Other Test *(Specify Below)*	Result	Specimen Collection Date (dd MMM yy)

2.3 Version

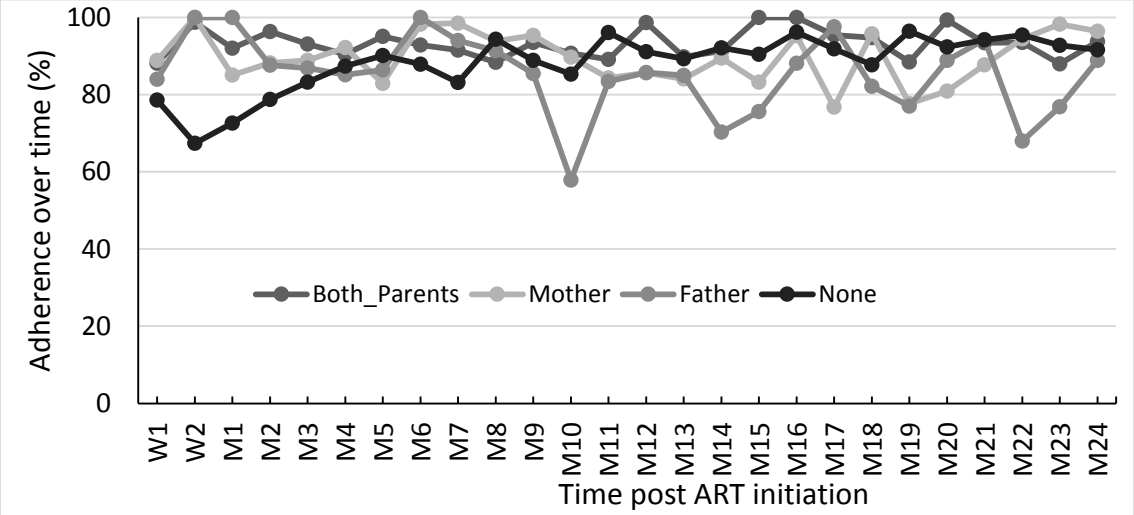
Staff Initials

Date dd MMM yy

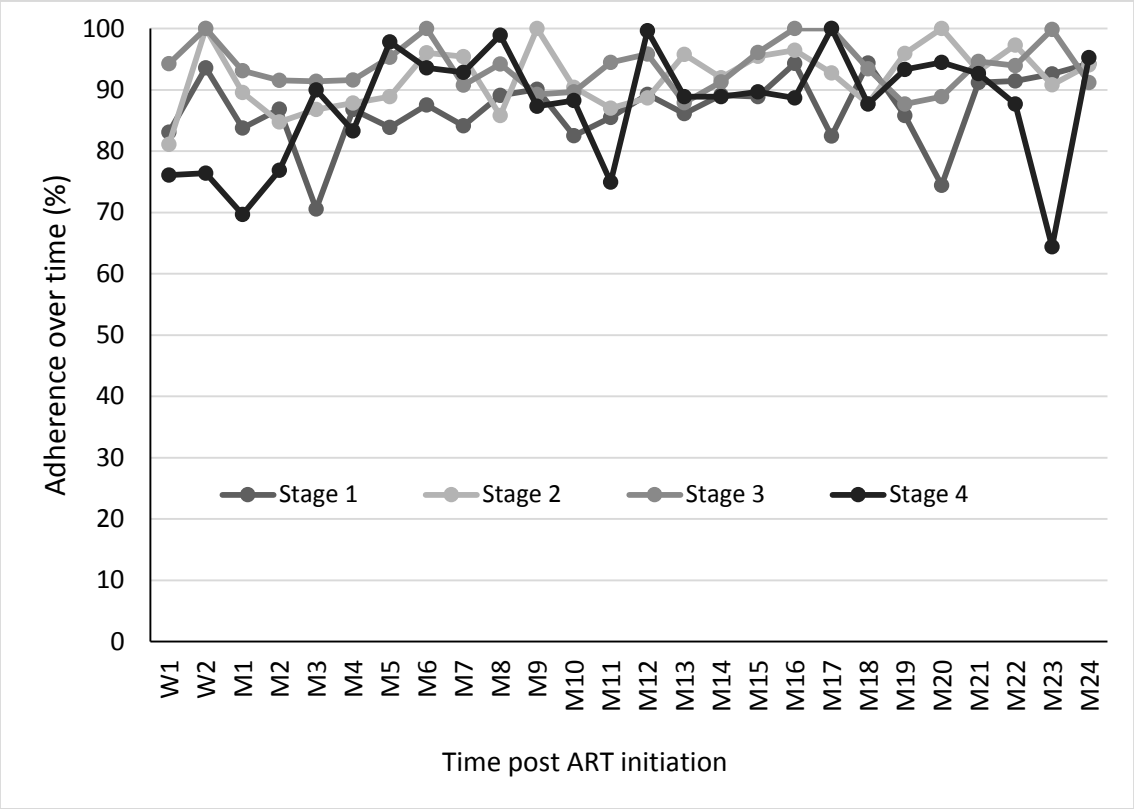
Appendix O: Supplementary data analysis



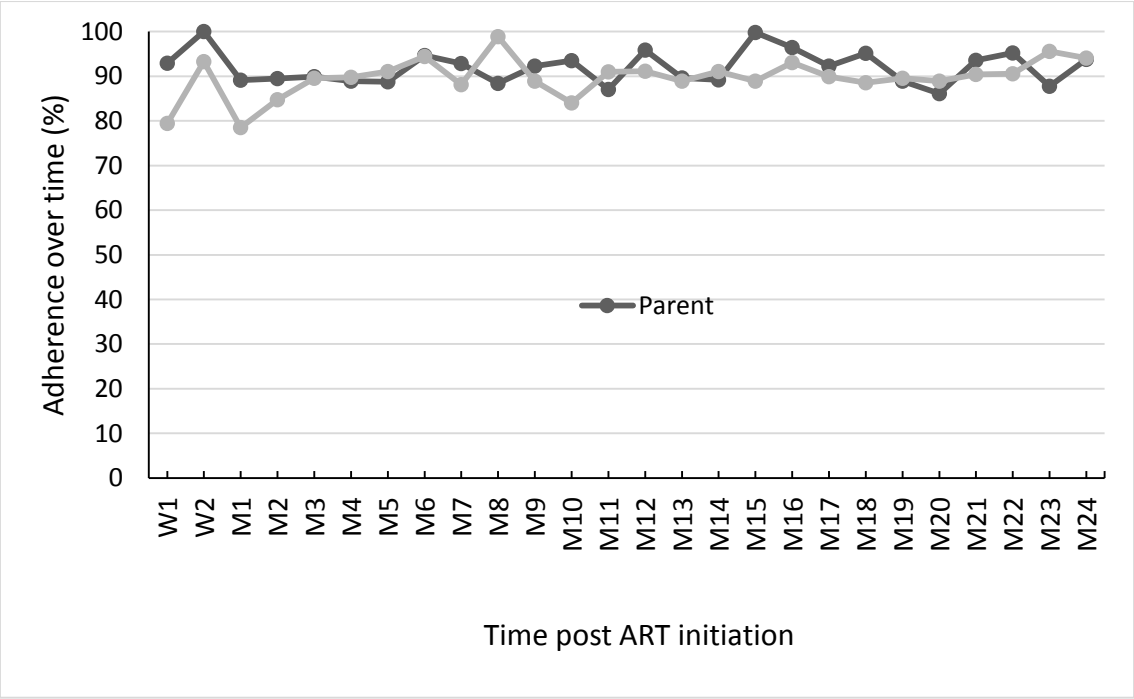
Median adherence over time (Gender)



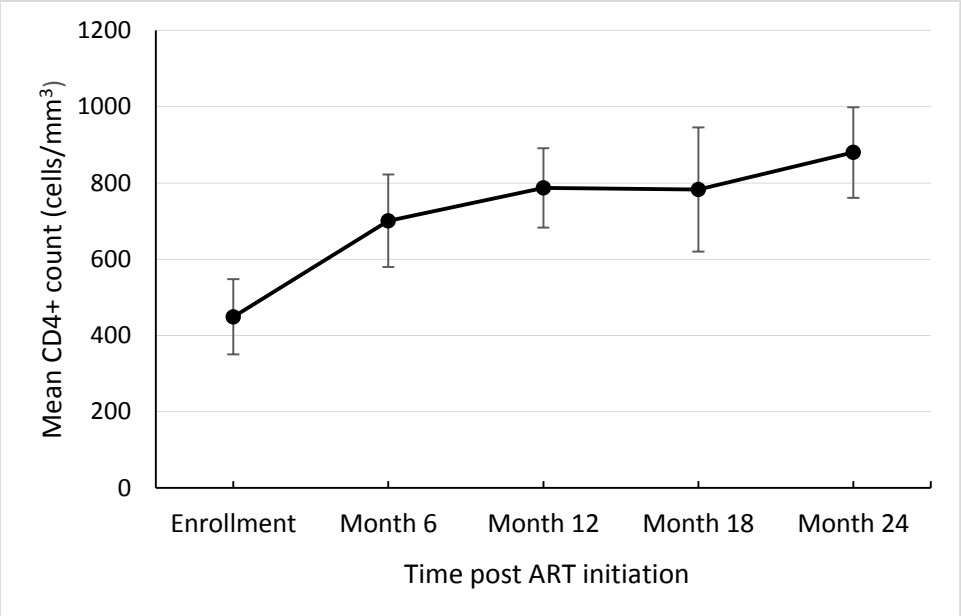
Median adherence over time (Which parent is alive?)



Median adherence over time (WHO stage)



Median adherence over time (Primary caregiver)



Mean CD4+ count over time with 95% Confidence Interval