Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study

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DECLARATION

I, Mary-Ann Davies, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part thereof has been, is currently being, or is to be submitted for another degree at this or any other university. I further declare that this work was not published prior to my registration for the degree of Master of Medicine in Public Health Medicine.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents of this dissertation in any manner whatsoever.

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Finally, I would like to thank the children and caregivers who participated in this study, whose dedication and commitment humbles me.

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LIST OF ABBREVIATIONS

3TC - lamivudine

ART – antiretroviral therapy

AZT – zidovudine

CDC – Center for Disease Control

CGSR – caregiver self-report

d4T – stavudine

DOT – directly observed therapy

EFV – efavirenz

FA – fully adherent

FDC – fixed-dose combination

HIV – human immunodeficiency virus

IAS – International Aids Society

IQR – interquartile range

LMIC – low- and middle-income countries

LPV/r – lopinavir/ritonavir

M. Med – Master of Medicine

MEMS - Medication Event Monitoring System

MR – medication return

NRTI – nucleoside reverse transcriptase inhibitor

NNRTI – non-nucleoside reverse transcriptase inhibitor

NFA – not fully adherent

NVP - nevirapine

OR – odds ratio

PACTG - Paediatric Aids Clinical Trials Group

PMTCT – prevention of mother to child transmission

PI – protease inhibitor

RCT – randomised controlled trial

RTV – ritonavir

SD – standard deviation

TDM – therapeutic drug monitoring

VAS – visual analogue scale

VL – viral load

WHO – World Health Organization

INTRODUCTION

1. DISSERTATION REQUIREMENTS

This work is being submitted in accordance with the revised dissertation requirements for the degree of Master of Medicine (MMed) in Public Health Medicine as adopted by the University of Cape Town in 2009 (Dean's Circular MED12//09). These require that when submitting an MMed dissertation in the form of a published or publishable manuscript, the dissertation comprise the following components:

- Part A: Study protocol.
- Part B: Structured literature review.
- Part C: Study results in the form of a manuscript of an article for a named peer reviewed journal.
- Part D: Supporting documents including data capture instruments, consent forms, ethics approval letter and technical appendices.

2. HISTORY OF DISSERTATION AND ROLE OF CANDIDATE

This study was conceived in 2002, when I was registered for individual courses for the degree of Master of Public Health. I was responsible for the design of the study including development of data collection tools for adherence monitoring and a database for storage of adherence information under the supervision of B. Eley. This study formed part of a larger cohort study of antiretroviral therapy for the treatment of HIV-infected children and their infected parents at Red Cross Children's Hospital, for which ethical approval was obtained. (Annexures A and B).

Hence there was no separate proposal for the adherence study, and no separate ethical approval was needed. I participated in patient enrolment and data collection which occurred between July 2002 and February 2005. In 2006 I registered for the full degree of Master of Public Health and in 2007 revised this registration to that for the MMed (Public Health Medicine). Under the supervision of B. Eley and A. Boulle, I conducted the main analysis work in 2007 and wrote the final manuscript which was submitted to BMC Pediatrics in February 2008. The paper was accepted and published in September 2008. As I still had to complete a further 2 years of registrar training, the dissertation is being submitted in April 2010 as a requirement for admission to the Public Health Medicine examination of the College of Medicine of South Africa.

3. CONTENTS OF THE DISSERTATION

In accordance with the regulations for the MMed (Public Health Medicine) dissertation, this work contains the following sections:

Part A: Study protocol: This was prepared in 2007 to cover the analysis of the adherence data which had already been collected as part of the broader research study described above. The literature review and study justification contained in the protocol therefore apply to early 2007, the data collection procedures describe how the data to be analysed had already been collected at that time, and the proposed analysis is described prospectively. Footnotes have been inserted into the original protocol to indicate where any deviations from the protocol have been made during the course of the analysis.

Part B: Structured literature review of paediatric antiretroviral adherence studies from lower and middle income countries. The literature review is presented in two parts:

- Part B (i): Main literature review covering studies published prior to submission of this paper for publication in February 2008.
- Part B (ii): Post-script literature review covering studies published from 1 February 2008 to 31 Januray 2010. This has been included as the dissertation is being submitted after publication of the manuscript in order to update the literature review and contextualize the findings of this study within current paediatric antiretroviral adherence research.

Part C: Manuscript as published in BMC Pediatrics. The tables and figures that comprise the article are numbered as they appeared in the article and thus do not appear in the list of tables and figures for the dissertation as a whole.

Part D: Supporting documents as follows:

- Protocol for study of antiretroviral therapy for children at Red Cross Children's Hospital South Africa of which this study is one component. This has been abridged by omitting sections not relevant to this study, but includes consent forms, and data collection instruments.
- Official ethics approval letter from the University of Cape Town Faculty of Health Sciences Research Ethics Committee.
- Instructions to authors for the target journal, BMC Pediatrics.
- Technical appendix explaining choice of adherence measure used in study.

PART A: PROTOCOL

1. SYNOPSIS

Title: Assessment of adherence to antiretroviral therapy in young children in Cape Town, South Africa measured by medication return and caregiver self-report: a prospective cohort study.

Background and Rationale: Excellent adherence to antiretroviral therapy (ART) is necessary if HIV-infected children are to experience the dramatically improved outcomes that this treatment affords. However, there is very limited data on adherence to antiretroviral therapy in Africa, with few studies that examine the predictive value of low technology measures of adherence in terms of viral and immune outcomes. In addition there are no long terms studies of adherence in young children in Africa.

Objectives: To determine the association between adherence to ART in young children throughout the first year of therapy measured by medication returned as well as caregiver self-report, and subsequent virologic and immunologic outcomes, and to identify predictors of good long-term adherence.

Study design, population and sampling: This is a prospective cohort study, analyzing existing data collected on 122 HIV-infected children who commenced ART at Red Cross Children's Hospital in Cape Town. During the first year of treatment, adherence was measured monthly at the clinic by medication returned, with viral and immune response assessed at the end of the year. After 3 months of treatment, a questionnaire was administered to assess experience with

giving medication and self-reported adherence. The association between measured adherence and immune and viral response will be determined using logistic regression models to adjust for other predictors of these outcomes. Similarly, multivariate logistic regression will be used to identify predictors of good adherence.

2. BACKGROUND AND SIGNIFICANCE

In 2006, UNAIDS estimated that there were 2.3 million HIV-infected children under 15 years worldwide, with 85% of these living in sub-Saharan Africa.[1] South Africa was estimated to have 294 000 HIV-infected children <15 years of age at mid-2006.[2] Antiretroviral treatment (ART) of children in Africa has resulted in dramatically improved survival, clinical, immunologic and virologic status in the few reported cohorts with treatment access.[3-9] Excellent adherence is the most important factor in determining treatment success and preventing viral resistance, and the need for near-perfect adherence to lifelong therapy from an early age has been identified as a major challenge in the administration of ART to HIV-infected children.[10-14] There is concern about the extent to which such adherence is achievable for children in resource-limited settings, particularly in the context of the rapid scale-up of paediatric treatment programmes required to address the HIV burden on children in Africa where <15% of children needing ART on the continent currently receive it.[10, 12, 15-16]

Research from rich countries suggests that adherence may be more complex in children compared to adults due to many factors including reliance on caregivers who may themselves be ill or may not be the child's parent, complex dosing regimens, lack of availability of paediatric fixed-dose combinations (FDC), poor drug palatability, difficulty with taking tablets/capsules and interference with daily routines such as schooling, mealtimes and sleep.[13, 17-22] These studies report adherence estimates of between 50 and 75%, well below the required 90 to 95% to achieve optimal viral suppression.[11, 13, 17-22] Interpretation of studies on paediatric adherence is furthermore complicated by the lack of consistency in

methods of assessing adherence and discrepant definitions of adherence.[22] In addition, although it has been suggested that multiple measures of adherence should be used to assess adherence, the majority of studies make use of a single measure, caregiver self-report, which is known to over-estimate actual adherence.[22]

While African adult studies show that good adherence is possible despite poor social circumstances, there are limited studies in children.[15, 23] Health service challenges as well as individual factors such as poor socio-economic circumstances, poor literacy and the prohibitive cost of liquid drug formulations necessitating tablet administration to very young children may be further barriers to good adherence in African children.[10, 12] Muller et al.[24] used the electronic Medication Event Monitoring System (MEMS) to measure adherence for a 3 month period in young children in South Africa (median age 48 months) and found median adherence of 87.5% (IQR: 69 – 97). However, only 36% of patients achieved excellent (≥95%) adherence. In contrast, 91% of caregivers reported excellent adherence on a visual analogue scale (VAS).[24] MEMS adherence correlated significantly with attaining virologic suppression, while VAS adherence was less predictive.[24] In Kampala, Uganda, similarly discrepant results are reported using different adherence measures.[25] Among children aged 2-18 years 72% had adherence ≥95% measured with home-based unannounced pill counts, compared to 89% using 3-day self-reported adherence and 94% using clinic-based pill counts.[25] This underpins the need to use multiple measures of adherence to obtain accurate estimates. The only other dedicated ART adherence studies of African children only measured self-reported adherence and included only older children, with approximately one

third of caregiver-child pairs reporting missing doses in studies in both Côte d'Ivoire[26] and Uganda[27].

African studies thus concur with international literature that more objective measures of adherence (e.g. unannounced pill counts and MEMS) tend to be more sensitive to lapses in adherence.[22, 28] However, apart from the single South African study, the association between each of these measures of adherence and treatment outcomes has not been determined. In addition, measures such as MEMS and unannounced pill counts are not feasible in resource-limited settings with large-scale programs, and there is a need to determine the utility of simpler measures of adherence such as clinic-based pill-counts and self-report in predicting virologic response in the African context. Furthermore, all published African studies have been conducted over short periods (≤3 months), mostly in older children and may not reflect longer term adherence patterns in very young children.

There is thus a need for further studies on adherence to ART in children in Africa, particularly longer term studies on very young children, using more than one measure of adherence, in order to determine both levels and determinants of adherence, and the relationship between measured adherence and treatment outcomes. In particular, it would be useful to be able to identify children at greatest risk of sub-optimal long-term adherence in the context of busy clinics carrying out rapid scale-up ART roll-out programmes, so that adherence support can be appropriately directed.

3. AIM

To determine the association between adherence to ART in children throughout the first year of therapy measured by medication return (as measured at the clinic) (MR) as well as caregiver self-report and subsequent virologic and immunologic outcomes, and to identify predictors of good long-term adherence.

4. OBJECTIVES

1. To describe clinical and socio-demographic characteristics of children commencing ART at Red Cross Children's Hospital.
2. To describe the level of adherence to ART in children throughout the first year of treatment using medication return (MR), as well as after 3 months of treatment using caregiver self-report.
3. To assess the extent of agreement between self-reported adherence and measured MR adherence for the same period.
4. To determine the association between each of the above measures of adherence and virologic and immunologic outcomes.
5. To identify factors associated with good adherence during the first year on ART.
6. To describe caregiver experience with administering ART to infants and young children.

5. METHODS

This study will make use of data collected prospectively by the Red Cross Children's Hospital ART programme. The data was collected as part of clinical care of children commenced on donor-funded ART prior to the Western Cape provincial government roll-out of ART. The principal objectives of this programme were to extend access to ART to as many children and their parents as possible, and to evaluate ART effectiveness and adherence locally.

5.1 Study design

Prospective cohort study

5.2 Population and sampling

All HIV infected children (n=122) commenced on antiretroviral triple therapy between July 2002 and January 2004 will be included in the study. Selection criteria for commencement of ART are detailed in the original programme protocol and published research (Annexure A).[4] Briefly, clinical and immunological criteria as recommended by the 2001 European treatment guidelines were followed, in addition to selective social criteria that assessed treatment readiness and caregiver willingness to comply with monitoring.[29] These included having an identifiable caregiver to administer medication and attend clinic appointments; being resident in Cape Town for at least 3 months and caregiver compliance with the last 3 clinic appointments.

The majority of children were commenced on stavudine (d4T), lamivudine (3TC) and efavirenz (EFV - children >10kg or >3 years) or ritonavir (RTV - children <10kg or <3 years).

5.3 Sample size

At the time of data collection, there were no studies from resource limited settings that examined the association between adherence and virologic or immunologic outcomes on which to base a sample size calculation. It was anticipated that more than 100 children would commence ART and be included in the study, which would make it the largest dedicated pediatric ART adherence study to date from either a developed or developing country.[22][*]

5.4 Measurements

Analysis of the following existing measurements that were taken as part of the ART programme will be done:

[*]The change from donor-funded ART to the government ART programme necessitated ending the study as the government programme did not fund adherence monitoring. We therefore made use of all existing data on children who initiated ART during the study period. The accumulated sample size comprised 88 children who remained alive and in care at 1 year when viral load measurement was performed, all of whom had adherence assessments done. This was sufficient to detect a 50% reduction in the proportion with viral suppression in those with adherence below the selected threshold for "good adherence", compared to those with adherence above this threshold with 90% power, assuming that 75% of children would have adherence above the threshold and 80% of these children would be virologically suppressed.

5.4.1 Clinical and socio-demographic characteristics

Clinical and demographic characteristics at commencement of ART were recorded by the clinician treating each child using standardized data collection forms (Appendix 5 of Annexure A). As the Center for Disease Control (CDC) clinical staging system was used in data collection (Appendix 1 of Annexure A), for this analysis children will be retrospectively re-staged according to primary medical record information using the WHO 4-stage clinical classification.[30] Weight-for-age, height-for-age and weight-for-height z-scores will be calculated using EpiInfo 2000, version 1.0 (Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia).

5.4.2 Laboratory measurements

Viral load, CD4 cell count and percentage were determined using standard laboratory methods at commencement of ART and after 1 year of treatment (Appendices 5 and 12 of Annexure A). Viral suppression will be defined as <400 copies/ml.

5.4.3 Measurements of Adherence

A. Medication return (MR)

At every monthly visit for 1 year, caregivers were requested to return all empty medicine containers together with unused medication. A dedicated programme pharmacist measured the amount of unused medication volumetrically for syrups/solutions and by pill count for tablets/capsules. The percentage adherence for each antiretroviral medication was calculated by dividing actual use (determined from returned containers and unused medication) by expected

use (determined from the previous month's script), and entered on a standard form. (Appendix 7 of Annexure A) These measures have been entered into a Microsoft Excel spreadsheet as a monthly percentage adherence for each individual drug.

B. Questionnaire

A standardized interview (Appendix 8 of Annexure A) was administered by the treating clinician to each caregiver after the child had completed 3 months of ART. The interview script was based on Pediatric AIDS Clinical Trials Group (PACTG) adherence questionnaires modules 1 and 2.[31-32] The interview assessed the caregiver's ability to accurately describe the ART regimen, recall of missed doses in the past 3 days, difficulties associated with giving medication and beliefs about ART. Interpreters were used so that interviews were conducted in the language of the caregiver's choice. Caregiver responses were recorded on a standardized data collection form (Appendix 8 of Annexure A) and anonymously entered into a password protected Microsoft Access Database.

5.5 Data Management

Clinical and socio-demographic characteristics as well as laboratory measurements have been entered into a Microsoft Excel spreadsheet. MR measurements have been stored in a separate Microsoft Excel spreadsheet, while adherence questionnaire responses have been entered into a Microsoft Access database. These 3 sources of data are all anonymized and will be merged using the anonymization key into a single password-protected Microsoft Access database. Hard

copies of completed data collection forms will remain stored in locked steel filing cabinets in locked offices.

6. ANALYSIS:

All statistical analysis will be carried out using Stata (version 9) (Stata Corporation, College Station, Texas, USA).[†]

Continuous variables will be summarized using means and standard deviations (SD) for normally distributed data and medians and IQRs for non-normally distributed data. Categorical variables will be described using proportions.

Medication return (MR) adherence data will be examined to determine the best way of developing a composite measure of adherence for all three drugs over the year. The correlation between viral suppression at one year and both the monthly mean adherence for all 3 drugs and the lowest monthly adherence of any drug will be calculated using longitudinal logistic regression analysis methods. In addition, the relationship between viral suppression and a simple overall mean annual adherence for all 3 drugs will be determined using logistic regression to adjust for other factors that might determine viral suppression. A small amount of extra medication (in excess of what was prescribed) was issued at each visit so that patients

[†] Stata (version 10) became available before the analysis was commenced and was thus used.

would not be without medication if drugs were spilled or additional doses required due to vomiting or spitting out. For a number of medication returns, therefore, more drug was used than prescribed (i.e. adherence >100% is recorded). For these visits, adherence will be capped at a maximum of 100% per return when calculating monthly and annual mean adherence. Factors associated with adherence >100% will also be examined.

The best composite measure of MR adherence will be selected based on prediction of viral suppression, clinical interpretability and simplicity. Using this composite measure, the cut-off level of adherence that best predicts viral failure will be determined. Adherence above this threshold will be called "good adherence".

Univariate and multivariate analysis of the association between demographic, social and clinical factors, as well as experiencing problems with giving medication, and having "good adherence" will be examined. For univariate analysis, Wilcoxon rank sum (Mann-Whitney) and Student's t-tests will be used for non-normally and normally distributed variables respectively and chi^2 or Fisher's exact tests for categorical variables according to the expected number of observations within each cell. Logistic regression models will be used for multivariate analysis.

Based on interview responses to doses missed in the last 3 days, children will be classified as either fully adherent (FA) (no doses missed) or not fully adherent (NFA) ($\geq$1 dose missed). Correlation between FA and viral suppression will be determined using logistic regression.

Agreement between MR adherence for the third month of treatment below the cut-off required for viral suppression, and caregiver reported NFA will be measured using the kappa statistic.

All multivariate models will be built by sequentially adding the next most significant predictor variable from the univariate analysis, and variables with a p-value <0.1 after adjustment for those already included in the model, or that change the OR for variables included in the model by more than 10%, will be retained.[‡] P-values for all statistical analyses will be reported exactly with no particular cut-off used to define significance.[34]

7. ETHICS, REPORTING AND IMPLEMENTATION

7.1 Ethics

This study has already been approved by the University of Cape Town research Ethics Committee as part of the larger study of ART in children (REC REF: 261/2002) (Annexure B). The latter study protocol specifically included collection of serial adherence data on children and use of this data for research. Voluntary written informed consent was obtained prior to study enrolment from each caregiver, together with verbal assent from the child if he/she was old enough to provide this. Consent forms (Appendix 3 of Annexure A) were translated into English, Afrikaans and Xhosa, with interpreters being used so that the study could be fully

[‡]This approach has been superceded by work on causal inference that was published subsequent to completion of our analysis.[33]

explained to the caregiver and child in a language that they understood and all questions addressed.

Since the data to be analysed were collected as part of the routine clinical care of the children, there is no anticipated harm to the children. Every effort will be made to ensure patient confidentiality through the use of anonymization keys and password protection in the database to be analyzed, and the secure storage of all source documents.

Benefits to the children and their caregivers during the study period were enhanced adherence monitoring through the regular medication measurements and questionnaires, which may have improved clinical outcomes. As adherence monitoring was provided to all children in the same way, this possible benefit would have been afforded equally to all children in the study.

Results of this study could benefit all children commenced on ART as it may assist in development of clinical practice to prevent poor adherence as well as to identify children likely to be non-adherent and requiring adherence interventions, in the context of busy roll-out clinics where detailed adherence assessment and intervention is not practical for all children. As the children in the study group are representative of those for whom the research outcomes are intended, justice is maintained.

The study will be conducted in accordance with the 1996 Declaration of Helsinki and local rules and ethical regulations of South Africa.

7.2 Reporting and implementation

The results of this study will be submitted for publication in a peer reviewed journal and presented at local conferences and meetings so that they can be maximally accessed by those involved in providing ART for children. The clinicians and pharmacist who participated in the project and all clinicians involved in ART provision at Red Cross Children's Hospital will be informed of the results. Since these clinicians support outreach programmes to a number of paediatric ART sites in the Western Cape and are involved in developing provincial, national and international paediatric ART guidelines, there should be ample opportunity for the results to influence general paediatric ART policy and practice.

8. LOGISTICS

8.1 Timetable

Task	Duration
Merge, clean and check data sets	February – April 2007
Analysis	May – September 2007
Prepare draft manuscript	October – December 2007
Prepare final manuscript and submit for publication	January – February 2008

8.2 Budget

As the data has already been collected, no further costs will be incurred. Mary-Ann Davies will be responsible for data management and analysis of the merged database as part of her M.Med studies, and so does not require any payment.

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PART B (i): STRUCTURED LITERATURE REVIEW

1. INTRODUCTION

Paediatric ART guidelines universally recommend adherence monitoring and support, as near perfect adherence is required for optimal viral suppression and prevention of resistance.[1-9] Access to ART for children in low- and middle-income countries (LMIC) has expanded enormously in recent years with nearly 275,000 children on treatment by the end of 2008.[10] Adherence for children in developing countries with extremely limited access to second-line regimens, viral load measurement or resistance testing is critical.[11] In this context, the accurate measurement of adherence and identification of its determinants is important to maintain first-line regimens and develop appropriate adherence support.[12-14]

WHO defines adherence as the "extent to which a person's behaviour corresponds with agreed recommendations from a health care provider".[15] For young children, however, the role of the caregiver is important with adherence being a triadic partnership between medical team, caregiver and child.[16-17] The caregiver of an HIV-infected child may not be the biological parent, and may change over time.

This literature review will comprise two parts with the same objectives and search strategy.

- A main literature review that includes studies published before February 2008, when our study was submitted for publication.
- A post-script covering the period during and after submission of our paper (February 2008 – January 2010). This aims to update the review as well as contextualize and interpret our findings.

2. OBJECTIVES

This literature review aims to appraise all published observational studies of ART for HIV-infected children from LMIC that report a quantitative measure of adherence. The main review will include studies published prior to 31 January 2008, while the post script covers the remaining period to January 2010.

The objectives of the review are to report the following items as well as identify needs for further research:

- Methods used to measure adherence.
- Measurements of adherence in children.
- Agreement between measured adherence and immune or viral response to ART.
- Factors influencing adherence.

Adherence is context-specific. Challenges faced by a caregiver from an informal settlement in a developing country administering syrup to an infant may be very different from those of an adolescent responsible for their own adherence to pills in a wealthy country. The review therefore aims to be relevant to the context of adherence among very young children in Cape Town, South Africa. For this review, children will be defined as <14 years of age. This is consistent with National Treatment Guidelines[18], and adherence in adolescence is different to that in young children.[14, 19] Health service factors and access to treatment may influence adherence, hence limiting the review to LMIC.[17] Nevertheless, some challenges to adherence cut across settings and ages. Hence the review will draw selectively on quantitative paediatric adherence studies from high income settings, qualitative paediatric adherence studies and adult ART adherence literature.

3. SEARCH STRATEGY

A search of the Medline bibliographic database using the PubMed interface (National Library of Medicine, Bethesda, MD) was performed using the following strategy: "antiretroviral AND (child* OR pediatric OR paediatric) AND (adherence OR compliance)". A key word search was used as this yielded more studies than that of Medical Subject Headings. In addition, the bibliographies of reviews of paediatric adherence (identified through Medline as well as a search of International AIDS Society (IAS) conference abstracts between 2001 and 2007) were reviewed to identify additional studies.[17, 20-23] Articles from LMIC (as classified by the World Bank)[24] that reported at least one measure of adherence to ART in vertically HIV-infected children taking ≥3 ART drugs were included. Exclusion criteria were studies from high

income countries, inclusion of mostly adolescents, studies where most children were treated with <3 antiretrovirals, and studies of interventions to improve ART adherence, unless these included a measure of adherence in a non-intervention group. Published abstracts were reviewed to determine whether studies met the inclusion criteria.

4. ARTICLES PUBLISHED PRIOR TO FEBRUARY 2008

The search yielded 234 articles published prior to February 2008, of which only 16 met the inclusion criteria. An additional 2 studies were identified by searching the bibliographies of reviews.[21-22, 25-26] As there were only 18 studies that met the inclusion criteria (Table 1), no quality criteria were applied for inclusion, however study quality was appraised.

5. QUALITY AND COMPARABILITY OF STUDIES

Tables 1 and 2 summarize key features reflecting study quality and comparability. Quality criteria include whether the study primarily aimed to assess adherence, study design, sample size and selection criteria as well as the number and validity of measures of adherence.

Table 1: Characteristics of studies reviewed

a) Studies from Africa

Reference	Year of publication	Location & time	Design	Dedicated observational adherence study	sample size	Median (IQR) duration in months on ART at time of enrolment	Median (IQR) age in years at study enrolment	Regimens used
Fassinou[27]	2004	Côte d'Ivoire; 2000 - 2002	prospective cohort	No	78	79% enrolled at ART initiation	6.5 (0.7 - 15.2)[a]	2 NRTI + Nelfinavir (78%) or EFV (22%); 17% received drug as syrups
Eley[28]	2004	South Africa; 2002 - 2003	prospective cohort	No	80	All enrolled at ART initiation	50.5[b] (41.8 - 59.2)[c] months	D4T + 3TC+RTV or EFV
Arrivé[29]	2005	Côte d'Ivoire; 2004	cross sectional	Yes	112	NR	7.1 (4.7 - 10.9) (interruptions); 5.8 (2.4 - 7.9) (no interruptions)	2NRTI + Nelfinavir or EFV
Nyandiko[30]	2006	Kenya; 2002 - 2005	prospective cohort	No	279	All enrolled at ART initiation	6.0 (4.8 - 13.7)[c]	AZT + 3TC + NVP (<10kg) or D4T + 3TC + NVP (>10kg)
Bikaako-Kajura[31]	2006	Uganda; 2002 - 2003	cross-sectional	Yes	42	18	12	AZT + 3TC + EFV
Mukhtar-Yola[25]	2006	Nigeria; 2005	cross-sectional	Yes	40	NR	1-5 yrs: 57% 6-10 yrs: 33% 11-15 yrs: 10%	AZT or D4T+ 3TC+NVP
Reddi[32]	2007	South Africa; 2003 - 2005	retrospective cohort	No	151	All enrolled at ART initiation	5.7 (0.3 - 15.4)[a]	D4T + 3TC + EFV (over 3 years); D4T + 3TC + LPV/r or unboosetd RTV (under 3 yrs)
Wamalwa[33]	2007	Kenya; 2004 - 2005	prospective cohort	No	67	All enrolled at ART initiation	4.4 (1.5 - 12)[a]	AZT or D4T + 3TC + NVP (69%) or EFV (25%); some FDC use
Ellis[34]	2007	Malawi; 2004 - 2005	prospective cohort	No	238	All enrolled at ART initiation	87 (7 - 212)[a] months	Adult FDC only: D4T + 3TC + NVP
Nabukeera-Barungi[35]	2007	Uganda; 2004 - 2005	cross sectional	Yes	170	83% on ART for ≥ 1 year	10	FDC of D4T + 3TC + NVP (81%); FDC of AZT + 3TC + NVP (9%) ; FDC of AZT + 3TC with separate EFV (6%)
Muller[36]	2008	South Africa; 2006	prospective cohort over 3 months	Yes	73	28 (12 - 38)	48 (34 -65) months	2 NRTI + LPV/r (59%); 2 NRTI + NVP or EFV (32%) 2 NRTI + unboosted RTV (9%)

[a]range
[b]mean
[c]95% confidence interval
[d]standard deviation

NR: Not reported
FDC: Fixed-dose combination
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor

yr: year

b) Studies from LMIC outside Africa

Reference	Year of publication	Location & time	Design	Dedicated observational adherence study	sample size	Median (IQR) duration in months on ART at time of enrolment	Median (IQR) age in years at study enrolment	Regimens used
Bunupura-dah[37]	2006	Thailand; 2005	before and after trial of use of flavouring	No	30	NR	5.2[b]; 1.9[d]	2 NRTI + EFV or NVP or LPV/r; opened capsule, crushed tablet or liquid
Natu[38]	2007	India; NR	prospective cohort	No	25	All enrolled at ART initiation	6	Adult FDC only: D4T + 3TC + NVP
Safreed-Harmon[39]	2007	Thailand; 2004	cross-sectional	Yes	29	NR	6.1	NR
Myung[40]	2007	Cambodia; 2002 - 2004	retrospective record review	No	95	All enrolled at ART initiation	5.5[b]; 2.5[d]	D4T + 3TC + NVP or EFV
Pensi[26]	2007	India; NR	prospective cohort	No	21	All enrolled at ART initiation	<1yr: 1 1-5 yrs: 11 ≥6 yrs: 8	D4T + 3TC + NVP
Plipat[41]	2007	Thailand; 2003 - 2005	prospective cohort	Yes	162	on ART (62%) or starting ART (38%)	<7 yrs: 64%; 7-10 yrs: 22% 11-14 yrs: 14%	Dual NRTI (28%); 2 NRTI + NNRTI (65%) 2 NRTI + PI (7%)
Wachholz[42]	2007	Brazil; 2002	cross-sectional	Yes	194	40.2	6[b] (0.9 - 12)[a]	≥3 drugs (67%); 2 drugs (33%)

[a]range
[b]mean
[c]95% confidence interval
[d]standard deviation

NR: Not reported
FDC: Fixed-dose combination
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
yr: year

Table 2: Methods of measuring adherence and estimates of adherence

a) Studies from Africa

Reference	Number of methods of adherence measurement	Self report definition	Self report proportion with adherence above threshold	MR definition	MR proportion with adherence above threshold	Other definition	Other proportion with adherence above threshold	Correlation with clinical outcome
Fassinou[27]	1	Subjective caregiver experience of not having difficulty with adherence	79%					NR
Eley[28]	1			>85% pills/syrup used	"Most"			NR
Arrivé[29]	1	CGSR of no doses missed in previous month	67%					55% of adherent patient undetectable vs 0% non-adherent children (p=0.098); n=24
Nyandiko[30]	1	CGSR of no doses missed in previous month or 7 days	75%					No correlation with improvement in CD4%
Bikaako-Kajura[31]	1	Child and CGSR of never missing a dose	71%					NR
Mukhtar-Yola[25]	1	CGSR of taking >95% of doses	80%					NR
Reddi[32]	1	Monthly child or CGSR of missing no doses	60%					NR
Wamalwa[33]	1	CGSR of no doses missed in previous 2 weeks	64%					No correlation with virologic response
Ellis[34]	1	CGSR of >95% doses taken in previous month	90%					NR
Nabukeera-Barungi[35]	3	Child (if >12 years) or CGSR of ≥95% doses taken in previous 7 days	89%	≥95% pills used	home-based: 72%; clinic-based: 94%			NR
Muller[36]	2	CG VAS estimate of adherence over previous month				MEMS: >80% of doses taken	65%	74% of those with MEMS adherence >80% vs 43% of those with <80% adherence had viral load <50 copies/ml; (p=0.017); No correlation between VAS adherence and virologic response

NR: Not reported

b) Studies from LMIC outside Africa

Reference	Number of methods of adherence measurement	Self report definition	Self report proportion with adherence above threshold	MR definition	MR proportion with adherence above threshold	Other definition	Other proportion with adherence above threshold	Correlation with clinical outcome
Bunupuradah [37]	2	CGSR of no doses missed in previous 3 days	100%			Drug trough level in 10 children - repeated	1/20 trough levels low	NR
Natu[38]	1					% actual follow-up visits /expected	95% attendance	NR
Safreed-Harmon[39]	3 combined into single estimate	CGSR of no missed doses in previous month	100%	Average of pills used/pills prescribed	98 - 99%	Medical charts reviewed	NR	NR
Myung[40]	1	Report of no missed doses by child-care workers that administered DOT	99%					NR
Pensi[26]	1	CGSR of >95% adherence (no duration specified)	100%					NR
Plipat[41]	5	CGSR of ≥95% of doses taken in previous month; questionnaire of no doses missed in previous 3 days.	CGSR: 95% - 96% Questionnaire: 99%	≥95% pills used	84%	Physician assessment on VAS scale	55%	Mean log viral load decrease greater in those with ≥95% adherence by MR compared to those with lower adherence (p= 0.05); No correlation between CGSR adherence and virologic response;
Wachholz[42]	1	≥80% of doses taken in previous 24 hours	50.5%					NR

NR: Not reported

5.1 Primary aim of the study

Only 5 of 11 studies from Africa [25, 29, 31, 35-36] and 3 of 7 from other countries [39, 41-42] have the primary aim of assessing adherence. Most of the remaining studies report overall outcomes of a paediatric ART programme, with adherence being one of the outcomes reported. A single measure of adherence is used and methods of adherence assessment only briefly described. Studies by Bunupuradah et al.[37] and Myung et al.[40] report on adherence in the context of interventions, namely adherence before and after addition of a flavouring product to medication, and the use of directly observed therapy (DOT), with limited information on how adherence measurement was performed.

5.2 Study design

Adherence may fluctuate with duration on treatment and child's developmental stage, so cross-sectional and short term cohort studies have limited value unless children with a range of durations on ART are included.[17, 23] Apart from the study by Plipat et al.[41], however, the only long term cohort studies are those of paediatric ART outcomes, rather than of adherence per se. The latter studies follow children from ART initiation and adherence is assessed for up to a year or two after starting ART, and may be very different from that after longer durations of treatment. Furthermore, the very fact of routinely measuring adherence may impact on adherence itself, reducing the validity of measurements from later periods. In this respect, cross-sectional studies can actually "catch" patients at a range of treatment durations without affecting adherence by repeated measurement. However only 4 of 7 cross-sectional or short term cohort

studies report on treatment duration, with a mean/median between 18 and 40 months [31, 36, 42] or 83% of children on ART for ≥1 year [35]. Plipat et al.[41] uniquely included both children on ART (62%) and initiating ART (38%) in a 1 year follow-up cohort study, however adherence is not reported separately for long-term and new ART patients.

5.3 Sample size

The sample sizes range from 21 – 279, but are <100 in most studies. Only one study provided a sample size calculation.[42]

5.4 Methods of adherence assessment and definitions of "good/high" adherence

There is no gold standard for measuring adherence. Methods used can be direct such as therapeutic drug monitoring (TDM), or indirect. Indirect methods include child or caregiver self-report (CGSR) of doses missed, quantifying medication not used as a percentage of that prescribed, or electronically monitoring number and timing of instances of medication containers being opened. Proxies for indirect assessment of medication use are pharmacy refill records and clinic attendance. The anticipated biological effect of adherence in terms of viral or immune response can also be a measure of adherence, however the criteria for an immune response indicative of adequate adherence have not been defined in paediatric practice. A brief description of the threats to validity of the most commonly used measures will be provided.

Child or Caregiver self-report

This is commonly used in adult and paediatric studies as it is simple and cheap.[21, 43-44] Precisely for these reasons, it is the tool most feasible for measuring adherence in clinical practice in resource-limited settings, hence the importance of determining its validity. A meta-analysis of adult studies demonstrated that self-reported adherence is associated with virologic suppression and some paediatric studies from developed countries have shown similar associations.[45-48] Nevertheless CGSR may over-estimate adherence and is subject to recall and social desirability bias.[23] Most assessments ask about adherence in the last 1 to 7 days to limit recall bias, but this may miss patterns of non-adherence that are intermittent, for example over weekends or when the child and/or caregiver is away from home or ill. The impact of social desirability bias may depend on who administers adherence questionnaires as well as who provides the report, as a caregiver would not want to appear negligent, especially to the health care worker providing ART for her/his child. Van Dyke et al.[45] for example found that children themselves reported the lowest adherence, non-biological caregivers the highest, and biological parents an intermediate level.

Of the LMIC paediatric studies, 10 measure adherence using child or CGSR alone, with a further 5 employing this together with another method. Caregivers are the respondents for almost all studies and no studies report adherence separately for child respondents.[31-32, 35] Reporting period is mostly short but varies from the last 24 hours to the last month.

Medication return (MR)

This involves counting (pills) and measuring/weighing (syrups) medication not used, assuming that the remaining medication has been taken as prescribed. Medication return implies that assessments are done at the clinic. However home-based assessments, although resource-intensive, may be more accurate as they can be unannounced and don't rely on caregiver returns.[35] Children taking syrups may vomit or spit out medication, or syrup may be spilled so that MR may not accurately reflect actual drug ingested. In developed countries, there are few paediatric studies using MR and none in children taking syrups [21, 49].

Among studies in LMIC, adherence was assessed by MR in 4 studies.[28, 35, 39, 41] Only one study performed home-based measurements[35] and one assessed adherence to syrups.[28]

Electronic measurement of medication adherence

Electronic monitoring of opening of medicine containers by means of a microchip in the lid, is often considered the best of the indirect methods of measuring adherence.[43] However cost and technology requirements limit its use.[21, 23, 43, 50] Not surprisingly it was only used in 1 LMIC study.[36] Although it should provide a less exaggerated measure of adherence in comparison to other methods, the electronic monitoring device (usually in the form of the Medication Event Monitoring System (MEMS) cap of the container) is typically only used with one of the drugs and adherence for the others must be inferred. This may not be valid in children where poor palatability of a drug may affect adherence for that medication alone. In addition, Muller et al.[36] encountered a number of practical difficulties assessing the use of syrups with

MEMS caps designed for pill containers. The bottles tended to leak and with longer duration use, increasing amounts of syrup crystallized on the bottle neck and cap making opening and closing of bottles difficult.[36] Together with expense, these difficulties limit use for monitoring long term adherence in clinical practice.

Other indirect measures of adherence

Clinic attendance and physician assessment were each used in one study, with no study assessing adherence to pharmacy refills.[38, 41] These are all very indirect measures and have been infrequently used in adult studies as well as paediatric studies from developed countries.[21, 43, 51]

Therapeutic drug monitoring

This is the only direct measure of adherence but only assesses whether the last dose of the drug was taken. Furthermore, population reference values of antiretroviral medication in children are frequently lacking and drug levels may be influenced by differences in absorption, distribution and metabolism, as well as adherence.[52] Cost limits TDM use to small samples in research settings.[21] Indeed it was used in one LMIC study in only 10 children.[37]

Biological effect monitoring.

Measuring therapeutic impact in terms of viral load or CD4 response could be considered a method of assessing adherence itself. Most adherence studies, however, use this to assess validity of other adherence measures in terms of their association with CD4/viral response. Among the LMIC studies, however, only 5 actually assessed the validity of adherence measures in this way, and in many studies this was done for only a subset of children.[29-30, 33, 36, 41] While this impacts on study quality, poor access to CD4 and viral load measurement is a reality in most resource-limited settings, highlighting the importance of identifying other tools to monitor adherence.

Definitions of good/high adherence

There is no agreement on the threshold to define good adherence. While early adult studies suggested that adherence ≥95% was required to achieve viral suppression,[1] paediatric studies from high-income countries have defined good adherence using thresholds of 75% to 100% with an association shown between viral suppression and medication refill adherence as low as 75%.[51] Some studies report only mean/median adherence which has little meaning if the majority of patients are adherent.[39]

5.5 Selection of study participants and missing adherence measurement information

Long-term cohort studies

All long term prospective cohort studies included all children initiating or on ART in the respective programmes, however none report on the amount of missing adherence information, and only one explains how missing information for particular visits was dealt with.[30] In these studies adherence measurement was contingent on clinic attendance and it is unrealistic to assume that no clinic visits were missed. Furthermore children may not have been accompanied by a suitable caregiver to complete the CGSR or not returned their medication bottles. Nyandiko et al.[30] actually indicate that children were frequently not accompanied by their primary caregivers impacting on reliability of the CGSR. In this study, pill count or syrup volume measurement was used to supplement such possibly unreliable adherence assessments.[30] It is likely that other studies would have encountered the same problem.

Cross-sectional and short-term cohort studies

Most cross-sectional and short term cohort studies recruited only a subset of children on ART in the program, with sequential enrolment of those attending the clinic with their caregiver and consenting to participate.[29, 31, 35] The proportion of caregivers declining consent is only reported by Arrivé et al.[29] This is also the only study that reports on characteristics of those not included. Although Nabukeera-Barungi et al.[35] conducted both home-based and clinic-based pill counts, only children who attended the clinic with their medication containers were recruited at the outset. The Brazilian study is the only one where children were enrolled irrespective of clinic attendance with interviews conducted at home if the clinic visit was

missed.[42] It is probable that most studies over-estimate adherence as caregivers attending clinic visits and participating in studies are likely to be more adherent. Muller et al.[36] excluded children from orphanages, those with multiple caregivers and whose caregivers declined to participate.

5.6 Adherence measurement in the context of limited access to ART

As access to ART for children in LMIC has only recently expanded, all of these studies assessed adherence at times of very limited access. While this may have genuinely increased motivation to adhere, measures of adherence reported may be influenced by selection bias whereby patients most likely to be adherent were able to preferentially access treatment in limited programmes.[28] Furthermore, capacity for adherence counseling in early small programmes is far greater than scaled up programmes. In addition, social desirability bias may have a greater effect in the context of restricted ART access.

5.7 Summary of study quality appraisal

Ideally a good quality study should have an adequate sample size supported by a sample size calculation, avoid selection bias and include patients initiating as well as on ART for longer periods, have >1 measure of adherence and assess validity of measures through associations with viral load. No studies fulfill all these criteria, however those by Arrivé et al.[29], Nabukeera-Barungi et al.[35], Muller et al.[36], Plipat et al.[41] and Wachholz and Ferreira[42] match them most closely.

6. RESULTS FROM STUDIES REVIEWED

6.1 Characteristics of children studied

Most studies examined adherence predominantly in older children taking pills with the median/mean age ranging from 4 to 10 years. This mirrors the age at which children initiate ART in LMIC settings.[27-28, 30, 32-33, 53-56] In addition, as WHO recommended first-line regimens for children were non-nucleoside transcriptase inhibitor (NNRTI) -based, there are only small numbers of children on protease inhibitor (PI) -based regimens.[2, 27-28, 36-37, 41] This is an important concern as it is the liquid PI drugs of ritonavir (RTV) and lopinavir/ritonavir (LPV/r) that are notorious for their bad taste.[57]

6.2 Measurement of adherence

Estimates of adherence and methods of assessment used are summarized in Table 2. Eight of 11 studies from Africa and 4 of 7 from other LMIC used a single method of adherence assessment, while two studies used >1 method[30, 39] without reporting the results of each measure separately.

Child or caregiver self-report

This is the only measure for 10 studies and is used in combination with other methods in 6 studies. (Table 2) The cut-off s used to define good adherence by self report are high (95 – 100%), except in the Brazilian study (≥80% doses taken in the last 24 hours).[42] In African studies, proportions of children with good adherence range from 60 – 90%. Estimates from other LMIC are 95 – 100% of children with good adherence, except in the Brazilian study[42] where only 51% of children have good adherence. This is the only study that recruited patients irrespective of their clinic attendance and may provide a more accurate estimate of adherence. These estimates are similar to those from paediatric studies from developed countries which range from 34 – 100% "good" adherence by CGSR and 20 – 58% by child self-report using cut-offs of 90 – 100%.[21, 45-46, 58] They are also similar to adult studies from resource limited settings with proportions of patients with good adherence by self-report of 54 – 97%.[43-44]

Medication return

Estimates of adherence by MR are between 72% and 98%.[28, 35, 41] Interestingly, Nabukeera-Barungi et al.[35] found that 94% of patients had used ≥95% of pills when assessed at the clinic but only 72% when assessed at home, with clinic-based pill counts estimating higher adherence than clinic-based child or CGSR (89% ≥95% adherent). Both clinic-based measures had poor agreement with the home based measure suggesting that adherence is over-estimated with clinic-based measures alone.[35] While Ellis and Molyneux[34] intended to measure MR adherence in children taking fixed-dose combination tablets (FDC), in practice it was impossible to perform accurate pill counts for very young children taking fractions of tablets. There are few paediatric MR studies from developed countries with similar estimates of mean adherence of 70 – 90%.[21]

Electronic monitoring

Muller et al.[36] found that 65% of children took more than 80% of doses with only 40% being >95% adherent using MEMS caps monitoring. These measures suggested far lower adherence than the estimate of 91% of patients having ≥95% adherence obtained by CGSR using a visual analog scale (VAS).[36]

Other methods

Clinic visit attendance of 95% was reported by one study.[38] Physician assessment was also used in a single study with a low estimate of 55% of children being >95% adherent. [41] This was lower than measures obtained from other adherence tools in the same study. Bunupuradah

et al.[37] measured trough drug levels on 2 occasions in 10 of 30 children, in addition to CGSR, and 19 of 20 measurements were within the target range.

6.3 Use of multiple measures and correlation with biological effect monitoring

Five studies used >1 measure of adherence and almost all found that more objective methods such as electronic monitoring or MR provided lower estimates than CGSR.[35-37, 39, 41] More objective methods were also more likely to show an association with CD4 or viral load response in the few studies that assessed this.[29-30, 33, 36, 41] For example, the proportion of children with viral suppression was nearly double in those with MEMS adherence >80% compared to other children (p=0.017), while there was no correlation with CGSR VAS adherence.[36] Similarly, Plipat et al[41] found mean viral load decrease to be greater in children with ≥95% adherence by MR, compared to other children, but no association with any of the CGSR measures and poor agreement between all measures used.[41] Studies using CGSR alone all showed no association with viral load or CD4 response, however usually only a subset of children had viral load measurements and small sample size may have limited power. For example, in 24 children (of 112 studied) with viral load measurements, Arrivé et al.[29] found 55% of adherent children compared to 0% of non-adherent children had viral load <400 copies/ml, but this difference was not statistically significant.

6.4 Factors influencing adherence

Eight studies explored factors influencing adherence by determining a statistical association with adherence/non-adherence while nine listed facilitators and barriers to adherence or reasons for missing doses (Table 3). For convenience, these factors are grouped as those related to the child/caregiver, the medication and the health care system.[17, 59] However, factors do not necessarily fit into a single category. For example, lack of money for medication (child/caregiver factor) is related to the cost of treatment. In addition, many factors are influenced by broader issues - for example, complicated regimens and poor drug palatability (medication related) are the direct result of a context of limited access to child-friendly drugs (health care system related), while capacity for caregiver disclosure to children or other adults (child/caregiver related) is influenced by stigma and expected consequences of disclosure which are affected by the health care system as well as the broader social context.[60-61]

Table 3: Factors influencing adherence

Table 3 a) Factors statistically associated with non-adherence

	Studies showing positive association with non-adherence	Studies showing no association with non-adherence
Caregiver/child related		
Old age	Arrivé[29]	
Orphanhood		Nyandiko[30], Safreed-Harmon[39], Wachholz[42], Nabukeera-Barungi[35]
Non-disclosure or partial disclosure to child	Bikaako-Kajura[31]	Nabukeera-Barungi[35]
Social class		Mukhtar-Yola[25]
Caregiver responsible for only 1 child	Wachholz[42]	
Caregiver not using ART themselves	Wachholz[42]	Nabukeera-Barungi[35]
Non-institutionalized children	Wachholz[42]	
Poor caregiver education	Wachholz[42]	Nabukeera-Barungi[35]
Children sicker at ART initiation	Nabukeera-Barungi[35]	
Caregiver disclosure to other people	Nabukeera-Barungi[35]	
Medication related		
Receiving EFV	Arrivé[29]	Nabukeera-Barungi[a][35]
Receiving LPV/r vs NNRTI		Muller[36]
Duration of treatment	Nabukeera-Barungi[b][35]	Plipat[41]
Health system related		
Distance from hospital		Nabukeera-Barungi[35]

[a]No association between any medication regimen and adherence
[b]Non-significant trend to lower adherence with treatment duration >24 months

Table 3 b) Facilitators of and barriers to good adherence

Barrier/facilitator of adherence	Supporting studies
Caregiver related	
Barriers	
Child refusal/parent child conflict	Fassinou[27], Arrivé[29], Reddi[32], Bikaako-Kajura[31]
Multiple caregivers	Fassinou[27], Reddi[32]
Travelling	Fassinou[27]
Forgot	Arrivé[29], Mukhtar-Yola[25], Plipat[41]
Delay in renewing script / missed clinic visit	Fassinou[27], Arrivé, Reddi[32],
Lack of money for transport to clinic, buying medication or buying food	Bikaako-Kajura, Mukhtar-Yola[25], Reddi[32]
Sharing medication with siblings not on ART	Muhktar-Yola[25]
Incorrect dosing	Reddi[32]
Child asleep	Plipat[41]
Facilitators	
Use of reminders	Bunupuradah[37]
Caregiver adherence strategies	Bikaako-Kajura[31]
Medication related	
Barriers	
Bad taste	Bunupuradah[37], Plipat[41]
Vomiting medication	Reddi[32]
Complicated regimens	Reddi[32]
Prolonged treatment duration	Fassinou[27]
Facilitators	
Mix with juices, syrup or flavour-masking product	Bunupuradah[37]
Perceived benefit of drug	Bikaako-Kajura[31]
Use of fixed-dose combination drugs	Pensi[26]
Health system related	
Barriers	
Drug stockout	Arrivé[29]
Stigma	Bikaako-Kajura[31]
Cost of drugs / limited access to ART	Muhktar-Yola[25]
Facilitators	
DOT ART	Myung[40]
Family centered model	Reddi[32]

Caregiver/child-related

Two major concerns for optimal paediatric adherence in Africa are whether adherence is adversely affected by low socio-economic status as well as caregiver changes and inconsistent caregiving quality exacerbated by adult illness and mortality. No studies showed worse adherence among children who had lost a biological parent, however this may reflect a selection bias as orphans with better caregivers are likely to access ART.[30, 35, 39, 42] Institutionalized children have been shown to have better adherence than those looked after by biologically related non-parent caregivers.[42] In Africa, however, most orphans would be cared for by extended families and it is a concern that having multiple caregivers is a common reason for non-adherence.[27, 32] Better adherence is associated with the child's caregiver being on ART or in HIV care him/herself, supporting family centered models of care.[32, 42] Results with regard to socio-economic status are mixed. Mukhtar-Yola et al.[25] found no association between social class and adherence, but all children were paying for ART so variation in social class may have been limited. In addition, lack of money for clinic transport, medication and buying food was cited as a reason for non-adherence in this and other studies.[25, 31-32] Not surprisingly, these were some of the few studies where at least some children included were required to pay for treatment. The impact of caregiver education is inconclusive.[35, 42]

Results regarding disclosure are also conflicting. Bikaako-Kajura et al.[31] found that disclosure to the child was beneficial enabling children to share responsibility for their own adherence. These findings have not been supported by other studies from LMIC as well as high income countries; however the inclusion of qualitative interviews in the former study may have provided

a better understanding of the impact of disclosure on adherence.[35, 47] Caregiver disclosure to other adults is associated with better adherence.[35]

As in developed countries, simply forgetting, child refusal of medication and interference with child's sleep are common reasons for missing doses, while reminders and other adherence strategies facilitated adherence.[17, 21, 27, 29, 31-32, 41, 60]

Medication related

Adherence to lifelong therapy is challenging, particularly with multiple poorly palatable drugs. Poorer paediatric adherence with longer treatment duration has been shown in developed countries.[62] Few studies from LMIC report on the influence of treatment duration with conflicting results, probably related to the duration on treatment of children included. While Plipat et al.[41] found no change in adherence over a year, Nabukeera-Barungi et al.[35] found a non-significant trend to lower adherence in those on treatment for >2 years and long duration was a barrier to adherence for children in Cote d'Ivoire.[27] As in developed countries, medication palatability was a reason for experiencing difficulty with giving medication in many LMIC studies.[37, 41, 46, 57] However, only Arrivé et al.[29] found a significant association between a particular drug and adherence. Nevertheless, the finding of similar adherence to the poorly palatable LPV/r compared to NNRTI-based regimens by Muller et al.[36] is questionable as MEMS monitoring was not done on LPV/r but assumed to be the same as that for the nucleoside reverse transcriptase inhibitor (NRTI) monitored. The overall high adherence rates reported by many studies may mask finding an effect of poor palatability. For example,

Bunupuradah et al.[37] found 100% adherence despite caregivers expressing difficulties with giving medication due to its poor taste. Almost all caregivers found it easier to give medication when a flavouring product was added, but the study could not show any increase in already perfect adherence.[37] Complicated regimens were considered a barrier to treatment with the use of FDC drugs facilitating adherence.[26, 32]

Health system related

Given the enormous differences in health system constraints between developed and developing countries, there is a paucity of data on the impact of health system factors on adherence in both adult and paediatric studies.[60] Drug stockouts were the most common reason for non-adherence found by Arrivé et al.[29], with the cost of drugs and limited access to ART being cited as barriers by Mukhtar-Yola et al.[25] Nabukeera-Barungi et al.[35] found no association between adherence and distance from clinic, but only children living within a 20km radius were included. Fear of stigma was a major reason for non-disclosure by caregivers to children.[31] While the exploration of interventions is beyond the scope of this review, Myung et al.[40] ascribe the high adherence in their study to the DOT strategy employed.

7. SUMMARY, INTERPRETATION AND NEEDS FOR FUTURE RESEARCH

This review shows that at the time of submitting our study for publication, there had been recent growth of LMIC paediatric ART adherence literature. However, there remained a dearth of good quality long term dedicated adherence studies using multiple measures of adherence validated with viral load. Studies of infants and young children taking PIs and syrups, were lacking. As in developed countries, study comparability was limited by the range of different methods and thresholds used to assess and define adherence, as well as different populations studied in terms of age, socio-economic context, access to and duration on ART and regimens used. While published studies indicated mostly good adherence from paediatric studies in LMIC, comparable with that of developed country settings, the use of predominantly self-report to measure adherence and the impact of a context of limited and or/early access to ART meant that these levels may not have reflected actual ART adherence in the long term as programmes scaled up. As access to viral load testing remained limited despite increasing access to paediatric ART, there was a need to develop practical low technology measures of adherence validated with viral response. Good quality cohort studies to increase understanding of short term and long term adherence, patterns of change in adherence over time, as well as the factors underlying adherence during different phases of ART, were also needed.

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PART B (ii) : POST-SCRIPT LITERATURE REVIEW

1. INTRODUCTION

In order to contextualize our research and ensure completeness of the literature review, studies published during and after the period of submission of our paper have been reviewed as a post script. This includes all studies published between February 2008 and January 2010 identified using the same search strategy and eligibility criteria as the main literature review. The search strategy yielded 124 articles of which 12 were eligible (including our own). One of these studies was excluded as it is a re-analysis of a study previously reviewed.[1-2] In addition, ongoing adherence research was carried out at Red Cross Children's Hospital resulting in a Doctoral dissertation, which has been included.[3]

2. NUMBER AND QUALITY OF STUDIES

The number of studies published in 2008 and 2009 (Table 4) reflects both increasing access to ART and recognition of the importance of studying adherence in developing country settings.[4-10] It is encouraging that study quality appears to have improved and the range of children's ages and regimens have widened. Sample sizes are ≥90 in all but 2 studies [11-12] with 4 very large studies with sample sizes of up to 1500 children.[13-16] Nine studies are dedicated adherence studies rather than reports of overall ART programme outcomes, with 4 of these including ≥6 months follow-up. Six studies used a single measure of adherence, namely child or

CGSR to assess adherence, with 2 studies using >1 method but not reporting on these discreetly.[16-17] In addition to our study where MR and CGSR was used to assess adherence, Vreeman et al.[13] supplemented CGSR with clinic attendance, while Michaels[3] used 4 adherence measures: CGSR, MR, pharmacy refill and clinic attendance. Nevertheless, only 3 studies determined validity of adherence measure with viral response, indicating ongoing restricted access to this technology.[3, 18-19]

3. RESULTS OF STUDIES REVIEWED

3.1 Characteristics of children studied

Most studies continue to include older children with the median/mean age ranging from 4.6 to 9 years (Table 4). Only the 2 studies from Red Cross Children's Hospital focus on younger children with median/mean age at enrolment of 37 and 27 months respectively.[3, 18] As expected, these are also the only studies where large proportions of children are on PI-based regimens and taking syrups. Michaels[3] reports 81% of children taking liquid formulations of drugs.

Table 4: Characteristics of studies reviewed (February 2008 - January 2010)

a) Studies from Africa

Reference	Year of publication	Location & time	Design	Dedicated observational adherence study	Sample size	Median (IQR) duration in months on ART at time of enrolment	Median (IQR) age in years at study enrolment	Regimens used
Davies[18]	2008	South Africa; 2002 - 2004	prospective cohort	Yes	115	All enrolled at ART initiation	37 (16 - 61) months	2NRTI + RTV or EFV
Michaels[3]	2008	South Africa; 2004 - 2006	prospective cohort	Yes	135	All enrolled at ART initiation	27[a] months	2NRTI + EFV (33%) or NVP (14%) or LPV/r (34%) or RTV (19%)
Biadgilign[14]	2008	Ethiopia; 2008	cross-sectional	Yes	390	24 (12 - 48)[b]	9 (1 - 14)[b]	D4T + 3TC + NVP (30%); AZT + 3TC + NVP (27%) AZT + 3TC + EFV (27%); D4T + 3TC + EFV (16%)
Vreeman[13]	2008	Kenya; 2003 - 2007	retrospective cohort	Yes	1516	58% on ART < 1 year	<1 yr: 2% 1-2 yrs: 18% 3-5 yrs: 29% 6-8 yrs: 24% 9-14 yrs: 27%	2 NRTI + NNRTI
Kiboneka[16]	2008	Uganda; 2004 - 2006	prospective cohort	No	770	377 (173 - 624) days	9 (4 – 13)	2 NRTI + NNRTI (98%)
Byakika-Tusiime[11]	2009	Uganda; 2004 - 2008	prospective cohort + cross sectional	No	41	NR	NR	NR
Vreeman[15]	2009	Kenya; 2007 - 2008	retrospective cohort	Yes	1490[c]	NR	5[a]; 3.5[d] pre-election; 6[a]; 3.2[d] post election	NR
Wamalwa[19]	2009	Kenya; 2004 - 2005	Unblinded RCT	Yes	90	All enrolled at ART initiation	4.7 (2.3 - 6.2)	2 NRTI + NNRTI
Polisset[20]	2009	Togo; 2006	Cross-sectional	Yes	74	10.5 (6.7 – 22.7)	6 (4 – 9)	2 NRTI + NNRTI (62%); 3 NRTI (32%); 2 NRTI + PI (6%)
Ntanda[17]	2009	Uganda; 2002 - 2008	retrospective review of prospectively collected data	No	101	All enrolled at ART initiation	6 (3 -10)	2 NRTI + NNRTI

[a]mean
[b]range
[c]number before election; 1408 after election
[d]standard deviation

NR: Not reported
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor

yr: year
RCT: randomized controlled trial

b) Studies from LMIC outside Africa

Reference	Year of publication	Location & time	Design	Dedicated observational adherence study	Sample size	Median (IQR) duration in months on ART at time of enrolment	Median (IQR) age in years at study enrolment	Regimens used
White[21]	2008	Jamaica; 2005	cross sectional	Yes	63	18.3 (8.3 - 32.6)	7.9 (4.8 - 10.6)	AZT + 3TC + NVP (81%)
Costa[12]	2008	Brazil; 2005	cross-sectional	Yes	54	NR	0.5 to 20[b]	NR

[a]mean
[b]range
[c]number before election; 1408 after election
[d]standard deviation

NR: Not reported
NRTI: nucleoside reverse transcriptase inhibitor
NNRTI: non- nucleoside reverse transcriptase inhibitor
PI: protease inhibitor

yr: year
RCT: randomized controlled trial

Table 5: Methods of measuring adherence and estimates of adherence (February 2008 - January 2010)

a) Studies from Africa

Reference	Number of methods of adherence measurement	Self report definition	Self report percentage with adherence above threshold	MR definition	MR percentage with adherence above threshold	Other definition	Other percentage with adherence above threshold	Correlation with clinical outcome
Davies[18]	2	CGSR of no doses missed in previous 3 days	86%	≥90% syrups/pills used	79%			≥90% MR adherence associated with VL <400 copies/ml aOR: 5.5 (95%CI: 0.8 - 35.6); No association between CGSR adherence and VL <400 copies/ml No association between CGSR or MR adherence and immunologic response
Michaels[3]	4	CGSR of no doses missed in previous 3 days	88%		Mean: 100-107%	% on time pharmacy refills: % on time clinic visits:	Mean: 85% Mean: 89%	CGSR adherence correlated with VL <400 copies/ml; No/weak association between other adherence measures and VL <400 copies/ml
Biadgilign[14]	1	CG SR of taking >95% doses correctly in previous 7 days	87%					NR
Vreeman[13]	2	Child or CGSR of taking all doses in previous 7 days	71%			Never missing a clinic vist	43%	NR
Kiboneka[16]	3 measures combined into single figure	CGSR of >95% doses taken in previous month	94%	>95% pills used	94%	>95% of pharmacy refills collected	94%	NR
Byakika-Tusiime[11]	2	CGSR	100%	>95% pills used in unannounced pill count	36%			NR
Vreeman[15]	1	CGSR of no doses missed in previous 7 days	98% pre-election; 95% after election					NR
Wamalwa[19]	1	CGSR of no doses missed in previous 2 weeks	85% (with diaries) 92% (no diaries)					>95% adherence associated with higher proportion of virologic suppression after 3 months, but not after 6 and 9 months of ART.
Polisset[20]	1	CGSR of no doses missed in previous month	42%					NR
Ntanda[17]	2 measures combined into single figure	CGSR of >95% of doses taken in previous 3 days	93%	>95% pills used	93%			

NR: Not reported VL: viral load

b) Studies from LMIC outside Africa

Reference	Number of methods of adherence measurement	Self report definition	Self report percentage with adherence above threshold	MR definition	MR percentage with adherence above threshold	Other definition	Other percentage with adherence above threshold	Correlation with clinical outcome
White[21]	1	Child or CGSR of no doses missed in previous 4 days	86%					NR
Costa[12]	1	Not mentioned	83%					NR

NR: Not reported

3.2 Measurement of adherence

Child or caregiver self-report

Cut-offs to define good adherence were between 95 and 100% of doses taken, and adherence estimates using this method are at least as good as those in earlier studies (Table 5). Barring 2 studies, the proportion of children with good adherence is ≥85%. Vreeman et al.[13] however reported a lower proportion of 71% while a worryingly low proportion of 46% was found in Togo.[20] Notably this study measured adherence both in clinic attendees and using home visits for those that did not present at the clinic, and is thus similar to the study by Wachholz and Ferreira[22] which also reported low adherence. The fact that drug stock-out was the reason for non-adherence for 43% of those missing doses in the Togo study nevertheless highlights the fact that adherence is critically dependant on a secure and reliable drug supply.[20]

Medication return

This was assessed in 5 studies, but is only reported independently of CGSR measurements in 3 with estimates of 79% and 88 – 100% of children having adherence ≥90% and >95% respectively[11, 18], while mean adherence of 100 – 107% is reported at 1, 2 and 6 month intervals by Michaels[3].

Other methods

Clinic attendance was assessed in 2 studies with very different results. Michaels[3] found that 90%, 79% and 70% of children in South Africa were on time for clinic visits at 1,2 and 6 months respectively, while Vreeman et al.[13] report that 57% of children missed at least one clinic visit,

although 76% of those missing a visit, missed less than 10% of their visits. These results may be explained by the differences in follow-up duration, however, as follow-up was limited to 6 months in the former study with a decline in adherence over time, while the latter study had a longer follow-up period and found the percentage of missed clinic visits increased dramatically after 6 months on ART. This underpins the need to incorporate ongoing adherence assessment into ART programmes. Pharmacy refill was only reported independently by one study with mean adherence of 85%.[3] No further studies have used electronic monitoring or TDM to assess adherence reflecting the limited access to these technologies in resource-limited settings.

3.3 Use of multiple measures and correlation with biological effect monitoring

While we found that CGSR of missed doses was more common in those with <90% MR adherence, CGSR non-adherence was only 32% sensitive for MR non-adherence and showed no relation to viral response.[18] In contrast, children with ≥90% adherence were 5.5 times more likely to have viral load <400 copies/ml compared to those with lower adherence after adjustment for disease severity. Michaels[3] also found poor agreement between the 4 measures of adherence studied, except that for clinic visits and pharmacy refill, and found that CGSR was most closely correlated with viral suppression. Differences between results from these 2 studies may be explained by the closer temporal relationship between CGSR and viral load measurement, different completeness of MR data and different treatment of MR adherence in excess of 100%, and the use of non-clinical staff to conduct CGSR interviews in the second study. Although Vreeman et al.[13] used 2 methods to assess adherence, agreement between methods is not reported and viral load measurements were not available. While White et al.[21]

only report on adherence by CGSR, they mention that better clinic attendance was associated with higher CGSR adherence. Wamalwa et al.[19] found that >95% adherence by self report was associated with viral load suppression after 3 months, but not after 6 and 9 months of ART, but the numbers of children with viral load measurements for the later time points is very small.

3.4 Factors influencing adherence

Ten studies report on factors statistically associated with non-adherence while 8 identify facilitators and barriers to good adherence (Table 6).

Table 6: Factors influencing adherence (February 2008 - January 2010)

a) Factors statistically associated with non-adherence

	Studies showing positive association with non-adherence	Studies showing no association with non-adherence
Caregiver/child related		
Female gender	Polisset[20]	
Old age	White[21]	Davies[18]
Orphanhood	Vreeman[13] (double orphans only)	White[21], Ntanda[17]
Non-disclosure or partial disclosure to child		Biadgiligin[14][a]
Non-institutionalized children	White[21]	
More than one HIV-infected child	Michaels[3]	
Poor caregiver education	Davies[18]	
Not taking cotrimoxazole with ART	Biadgilign[14]	
Receiving nutritional support	Biadgilign[14]	
Child awareness of caregiver's health status	Biadgilign[14]	
Poor socio-economic status	Davies[18], Michaels[3]	
Longer caregiver hours worked	White[21]	
Poor self-efficacy	Costa[12]	
Poor caregiver knowledge of medication regimen		Davies[18]
Caregiver depression	Byakika-Tusiime[11], Michaels[3]	
Use of medication diaries		Wamalwa[19]
Individual (vs compound) housing	Polisset[20]	
Medication related		
Duration of treatment	Vreeman[13], Michaels[3]	Davies[18][a], Wamalwa[19]
Receiving PI vs NNRTI-based ART	Davies[18], Polisset[20]	
Nausea as a side effect	White[21]	
Experiencing difficulty with giving medication	Davies[18], Polisset[20]	
≥ 6 pills/syrup spoons per day	Polisset[20]	
Health system related		
Not paying a fee	Biadgilign[14]	
Urban referral center	Vreeman[13]	
Post-election conflict	Vreeman[15]	
Counselling by clinician rather than counsellor	Michaels[3]	

[a]Negative association

b) Facilitators of and barriers to good adherence

Barriers/facilitators of adherence	Supporting studies
Caregiver related	
Barriers	
Child refusal / parent child conflict	Polisset[20]
Travelling	White[21]
Forgot	Biadgilign[14], White[21], Polisset[20], Michaels[3]
Delay in renewing script / missed clinic visit	Biadgilign[14], White[21]
Lack of money for transport to clinic, buying medication or buying food	Biadgilign[14], Ntanda[17]
Child asleep	Biadgilign[14]
Depression	Biadgilign[14]
Change in schedule	White[21], Davies[18], Michaels[3]
Facilitators	
Use of reminders	Davies[18], Michaels[3]
CG adherence strategies	Davies[18]
Seeing improved health of child	Byakika-Tusiime[11]
Medication related	
Barriers	
Bad taste	Davies[18], Michaels[3]
Vomiting medication	Polisset[20]
Health system related	
Barriers	
Drug stockout	Polisset[20]
Stigma	Ntanda[17]
Cost of drugs / limited access to ART	Ntanda[17]

Caregiver and child related factors

Effects of loss of one or both biological parents, socio-economic status and disclosure were examined by a number of studies. While Vreeman et al.[13] found that children who had lost both parents had worse adherence than those with one or both parents alive, other studies concurred with earlier literature finding no impact of orphanhood on adherence.[17, 21] Vreeman et al.[13] however, are the only researchers to consider whether children had lost one or both parents. Like Waccholz and Ferreira[22], White et al.[21] found children in institutions to have better adherence than those in family care settings. Both studies in Cape Town found better socio-economic status to be associated with adherence[3, 18], with lack of money for transport and medication being identified as barriers in other studies.[14, 17]

In contrast to the findings by Bikaako-Kajura et al.[23], non-disclosure to children and children's lack of awareness of the caregiver's illness were actually found to be associated with better adherence.[14] The latter study unsurprisingly found that adherence to non-ART medication was associated with adherence to ART, however the authors are unable to explain the unexpected association between receiving nutritional support and poor adherence.[14] It is however plausible that receiving nutritional support is a surrogate marker of lower socio-economic status.

Caregiver depression was associated with poor caregiver and child adherence.[3, 11] This is well described in adult studies.[24] The range of associations found with other caregiver and child factors such as better adherence for those living in compounds compared to those with

individual housing[20], variable relationships between child age and adherence[18, 21] and worse adherence with longer caregiver hours worked[21] highlight the need to explore context-specific factors influencing adherence. However, as in earlier studies, changes in schedule, simply forgetting and child refusal remain important barriers to adherence in all contexts including high income settings.[3, 6, 14, 18, 20-21]

Most caregivers continue to find use of reminders and other strategies to aid adherence helpful.[3, 18] Notwithstanding, Wamalwa et al.[19] specifically found that use of medication diaries had no impact on adherence and argue that availability of specific adherence enhancing interventions should not be seen as a prerequisite for successful ART.

Medication related factors

Unlike Muller et al.[2] who found no adverse effect of PI-based therapy on adherence, both our study[18] and that of Polisset et al.[20] found that receiving PI-based therapy was associated with worse adherence. This appeared to be related to experiencing difficulty with giving medication, and bad taste, vomiting and difficulty with administering large numbers of pills or syrup spoons were the most commonly experienced problems with PI drugs.[3, 18, 20]

The effect of increasing treatment duration yielded conflicting results. Wamalwa et al.[19] concurred with our finding of increasing adherence over time, while others have found the opposite.[3, 13, 18]

Health system related factors

The low adherence ascribed to drug stock-outs in Togo highlights the importance of health system factors in adherence.[20] Cost of drugs continues to be reported as a barrier to adherence, however Biadgilign et al.[14] found that those not paying a fee for their medication were more likely to be non-adherent and postulate that fee paying leads to caregivers placing greater value on their children's health. It is also plausible, however, that ability to pay a fee is a proxy for better socio-economic status, which has been shown to be associated with good adherence.[3, 18] Indeed the cost of drugs and limited access to ART were identified as barriers to adherence by Ntanda et al.[17] Vreeman et al.[13] found that children treated at urban referral centers were more likely to be non-adherent with clinic visits, demonstrating the impact of lack of access to nearby services on adherence. In a unique study by the same authors, adherence was shown to decrease during the conflict precipitated by the Kenyan presidential elections in December 2007.[15] Although adherence was high both before and after the conflict period (98% and 95% of children taking all doses respectively), the study demonstrates that adherence can be influenced by factors beyond the health system itself. Nevertheless, the fact that adherence was as high as 95% during the conflict period, and that adult studies have shown adherence to be maintained despite conflict, supports provision of ART despite political instability.[4, 25]

4. OTHER PAEDIATRIC ADHERENCE RESEARCH

Although the following studies did not strictly meet the criteria for inclusion in the post script literature review, their findings are pertinent to a consideration of paediatric ART adherence in LMIC. Muller et al.[1] performed a secondary analysis, and found that despite similar proportions of children with adherence >80% by MEMS monitoring on LPV/r-based and NNRTI-based regimes, a much higher proportion of children in the LPV/r group (77% vs 33%; p=0.002) achieved viral suppression. This concurs with adult studies that indicate that boosted PI regimens are more forgiving of non-adherence and high rates of viral suppression can be achieved with adherence as low as 80%.[26-27] While this should not lead to complacency with regard to adherence support, it indicates that better drugs, as well as better adherence, are the means to achieve optimal ART results.

A secondary analysis of a placebo-controlled trial of cotrimoxazole in the pre-ART era found that children with better adherence experienced lower mortality even if they were taking placebo.[28] It is postulated that good adherence is a proxy for better overall caregiving and the mortality benefit of adherence to placebo is ascribed to a "healthy caregiver" effect.[28] In terms of studies of adherence to ART, the validity of measures of adherence that demonstrate only small magnitude associations with clinical, viral load or CD4 response may be questionable, as small differences in biological effect may be due to better general caregiving by adherent caregivers rather than actual differences in drug exposure.

Finally, while qualitative studies were specifically excluded from this review, the Kenyan

investigation of factors influencing paediatric adherence through in-depth individual interviews and focus groups is worth mentioning for two reasons.[29] Firstly, while adherence was not actually measured in the study, admissions of non-adherence were frequent and indicate the likely over-estimation by routine clinic-based measures.[29] Secondly, an ecological model of paediatric ART adherence is postulated which highlights the interplay of child, caregiver, medication, health system and broader societal factors in influencing adherence.[29]

5. SUMMARY, INTERPRETATION AND NEEDS FOR FUTURE RESEARCH

The growing literature on paediatric ART adherence has paralleled the massively increased access to paediatric ART in LMIC in recent years,[30] with adherence estimates remaining reassuringly high. Nonetheless most studies in the current literature, even after consideration of those articles published recently, were conducted early on in scale-up programmes and may not reflect adherence as access expands, individual programmes treat increasing numbers of children and duration on treatment increases. We still lack an affordable, low technology, simple and practical tool with which to assess adherence on an ongoing basis. This is important as in busy programmes where most children are adherent, it may only be feasible to offer additional adherence support to those at high risk of non-adherence. Many CGSR questionnaires are time-consuming to administer in routine care. Further research is therefore needed to identify the key questions most sensitive for non-adherence as determined by "gold standards" such as electronic monitoring or viral response. The utility of a once-off MR adherence assessment as a second test to increase specificity in those identified as potentially non-adherent by CGSR should also be examined. Nevertheless, existing research suggests that even if refined, such tools will lack both

sensitivity and specificity, and the role of viral load monitoring should therefore be explored.[3, 18-19, 31] In this respect, a Thai adult study found that 30% of patients had an initial low detectable viral load when this technology became available within an existing ART programme.[32] In 92% of those patients, a reason for incomplete viral suppression could be identified and was usually associated with poor adherence.[32] With counseling, viral load became undetectable in 88% of patients and many resolved longstanding psychosocial problems.[32] The study demonstrates the potential utility of a simple blood test to identify patients in need of more intensive counseling and support, and the importance of increasing access to viral load testing.

There are still only a handful of studies of adherence in infants and young children taking syrups or PI-based therapy. While PI-based therapy may require less fastidious adherence, there is still a need to examine adherence in this population particularly as revised 2008 WHO guidelines promote initiation of ART in all infants irrespective of clinical or immune status, and PI-based therapy is optimal in children previously exposed to prevention of mother to child transmission (PMTCT) regimens.[33-34] Initiation and maintenance of adherence to potentially life-long therapy in an asymptomatic infant may pose unique challenges.

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PART C: MANUSCRIPT AS PUBLISHED IN BMC PEDIATRICS

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Research article

Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study

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Abstract

Background: Antiretroviral therapy (ART) dramatically improves outcomes for children in Africa; however excellent adherence is required for treatment success. This study describes the utility of different measures of adherence in detecting lapses in infants and young children in Cape Town, South Africa.

Methods: In a prospective cohort of 122 HIV-infected children commenced on ART, adherence was measured monthly during the first year of treatment by medication return (MR) for both syrups and tablets/capsules. A questionnaire was administered to caregivers after 3 months of treatment to assess experience with giving medication and self-reported adherence. Viral and immune response to treatment were assessed at the end of one year and associations with measured adherence determined.

Results: Medication was returned for 115/122 (94%) children with median age (IQR) of 37 (16 – 61) months. Ninety-one (79%) children achieved annual average MR adherence ≥ 90%. This was an important covariate associated with viral suppression after adjustment for disease severity (OR = 5.5 [95%CI: 0.8–35.6], p = 0.075), however was not associated with immunological response to ART. By 3 months on ART, 13 (10%) children had deceased and 11 (10%) were lost to follow-up. Questionnaires were completed by 87/98 (90%) of caregivers of those who remained in care. Sensitivity of poor reported adherence (missing ≥ 1 dose in the previous 3 days) for MR adherence <90% was only 31.8% (95% CI: 10.7% – 53.0%). Caregivers of 33/87 (38.4%) children reported difficulties with giving medication, most commonly poor palatability (21.8%). Independent socio-demographic predictors of MR adherence ≥ 90% were secondary education of caregivers (OR = 4.49; 95%CI: 1.10 – 18.24) and access to water and electricity (OR = 2.65; 95%CI: 0.93 – 7.55). Taking ritonavir was negatively associated with MR adherence ≥ 90% (OR = 0.37; 95%CI: 0.13 – 1.02).

Conclusion: Excellent adherence to ART is possible in African infants and young children and the relatively simple low technology measure of adherence by MR strongly predicts viral response. Better socio-economic status and more palatable regimens are associated with better adherence.

Background

Approximately 85% of the 2.3 million HIV-infected children under 15 years worldwide live in sub-Saharan Africa.[1] While antiretroviral therapy (ART) of children in Africa has resulted in dramatically improved survival, clinical, immunological and virological status, less than 15% of children needing ART on the continent currently receive it. [2-11] Excellent adherence is one of the most important factors in determining treatment success and preventing viral resistance, and the need for near-perfect adherence to lifelong therapy from an early age has been identified as a major challenge in the administration of ART to HIV-infected children.[10,12-15] There is concern about the extent to which this is achievable for children in resource-limited settings, particularly in the context of the rapid scale-up of pediatric treatment programs required to address the HIV burden on children in Africa.[14,16]

Research from rich countries suggests that adherence may be more complex in children compared to adults due to many factors including reliance on caregivers who may themselves be ill or may not be the child's parent, complex dosing regimens, lack of availability of pediatric fixed-dose combinations, poor drug palatability, difficulty with taking tablets/capsules and interference with daily routines. [13,17-23] Adherence estimates of 50 to 75% have been reported, well below the required 90 to 95% to achieve optimal viral suppression.[12,13,17-23]

While African adult studies show that good adherence to ART is possible despite poor social circumstances, there are limited studies in African children.[16,24-27] Health service challenges as well as individual factors such as poor socio-economic circumstances, poor literacy and the prohibitive cost of liquid drug formulations necessitating tablet/capsule administration to very young children are additional potential barriers to adherence in African children.[10,15] In Kampala, Uganda, 72% of children aged 2–18 years had adherence ≥ 95% measured with home-based unannounced pill counts, compared to 89% using 3-day self-reported adherence and 94% using clinic-based pill counts.[28] Muller et al. similarly found discrepant results using different measures of adherence in young children (median age 38 months) in South Africa.[29] Using electronic means (Medication Event Monitoring System (MEMS)) to monitor adherence, only 36% of patients achieved ≥ 95% adherence, in comparison to 91% of caregivers reporting excellent adherence on a visual analogue scale.[29] The only other published adherence studies of African children include only older children and measure self-reported adherence only, with varying results. In Côte d'Ivoire and Uganda, approximately one third of caregiver-child pairs reported missing doses and in South Africa, Reddi et al. describe 10% of children missing ≥ 3 doses during the previous month.[6,30,31] African studies thus concur with international literature that more objective measures of adherence (e.g. unannounced pill counts and MEMS) tend to be more sensitive to lapses in adherence.[21,32] However, such measures are not feasible in resource-limited settings with large-scale programs, and there is a need to determine the utility of simpler measures of adherence such as clinic-based pill-counts and self-report in predicting virological response in the African context. Furthermore, all published African studies have been conducted over short periods (≤ 3 months), mostly in older chidren, and may not reflect longer term adherence patterns in very young children.

We therefore aimed to measure the level of adherence to ART in infants and young children during the first year of treatment using both medication returned as measured at the clinic and caregiver self-report, to assess the extent to which such measured adherence predicts viral and immunological outcomes and to identify factors associated with good adherence.

Methods

Study design, setting and population

This was a prospective cohort study. All HIV infected children commenced on antiretroviral triple therapy between July 2002 and January 2004 (n = 122) as part of the ART program of the Red Cross Children's Hospital, a tertiary care institution in Cape Town, South Africa, were eligible and agreed to participate in the study. The ART program at the hospital began prior to the official national government ART program and was donor funded during this time. Selection criteria for commencement of ART have been described elsewhere.[2] Briefly, clinical and immunological criteria as recommended by the 2001 European treatment guidelines were followed.[33] In addition, the following limited social criteria needed to be met: having an identifiable caregiver to administer medication and attend clinic appointments; resident in Cape Town for at least 3 months; caregiver compliance with last 3 clinic appointments and caregiver willingness to comply with ongoing regular clinic attendance and monitoring. The majority of children were commenced on stavudine (d4T), lamivudine (3TC) and efavirenz (EFV – children >10 kg or >3 years) or ritonavir (RTV – children <10 kg or <3 years) as no other protease inhibitor was readily available in suitable formulation and dosage in South Africa at the time. Children were followed up with monthly clinical visits for the first year. Viral load, CD4 cell count and percentage were determined using standard laboratory methods at commencement of ART and after 1 year of treatment. The definition of undetectable viral load was <400 copies/ml. The study was approved by the University of Cape Town Research Ethics Committee [Ref: 261/

2002], and all parents provided written informed consent for their and their children's participation.

Measurements of adherence and associated factors

Clinical and socio-demographic characteristics at commencement of ART were determined by the clinician treating each child and recorded on standardized data collection forms. Children were retrospectively re-staged according to medical record information using the WHO 4-stage clinical classification for the purpose of this analysis.[15] Weight-for-age, height-for-age and weight-for-height z-scores were calculated with EpiInfo 2000, version 1.0 (Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia).

Measurement of adherence by medication return (MR)

At every monthly visit for one year, caregivers were requested to return all empty medicine containers and unused medication. A dedicated program pharmacist measured the amount of unused medication volumetrically for syrups/solutions and by pill count for tablets/capsules. The percentage adherence for each antiretroviral medication was calculated by dividing actual use (determined from returned containers and unused medication) by expected use (determined from the previous month's script).

A composite measure of annual average percentage adherence by MR was calculated by determining the arithmetic mean of the percentage adherence for each drug at each monthly visit. For caregiver-child pairs who did not return medication at every visit as requested, the annual average percentage adherence was calculated using the number of months for which medication was actually returned as the denominator when determining the arithmetic mean (per protocol analysis). Sensitivity analysis was additionally performed assigning adherence <90% for months in which medication was not returned and recalculating annual average percentage adherence for children with missing medication returns. A small amount of extra medication (in excess of what was prescribed) was issued at each visit so that patients would not be without medication if drugs were spilled or additional doses required due to vomiting or spitting out. For a number of medication returns, therefore, more drug was used than prescribed (i.e. adherence >100%) so adherence was capped at 100% per return when calculating annual average adherence. An uncapped annual average MR adherence was also calculated for some of the analyses.

Measurement of adherence by questionnaire

A standardized interview was administered by the treating clinician to each caregiver after the child had completed 3 months of ART. The interview script was based on Pediatric Aids Clinical Trials Group (PACTG) adherence questionnaires modules 1 and 2 and assessed caregiver's ability to accurately describe the ART regimen, recall of missed doses in the past 3 days, difficulties experienced with giving medication and beliefs about ART.[34,35] Based on reported missed doses, children were classified as not fully adherent (NFA) if ≥ 1 dose was missed in the previous 3 days. Interpreters were used so that interviews were conducted in the language of the caregiver's choice.

Analysis

All statistical analysis was done using Stata (version 10) (Stata Corporation, College Station, Texas, USA). The effects of low annual average (capped) MR adherence, average (capped) MR adherence in the month immediately preceding viral load measurement and reported NFA on viral load suppression and immunological response were determined using logistic regression models adjusted for other determinants of outcome. MR adherence was dichotomized as ≥ 90% or <90% as this threshold explained the largest amount of variability in the outcome. Univariate and multivariate analysis of the association between demographic, social and clinical factors as well as experiencing problems with giving medication and annual average MR adherence ≥ 90% were examined using Wilcoxon rank sum (Mann-Whitney), Student's t-test, chi^2 or Fisher's exact tests and logistic regression models as indicated. Agreement between MR adherence <90% and caregiver reported NFA was calculated using the kappa statistic.

All multivariate models were built by sequentially adding the next most significant predictor variable from the univariate analysis, and variables with a p-value <0.1 after adjustment for those already included in the model, or that changed the OR for variables included in the model by more than 10%, were retained. Since variables reflecting severity of illness (WHO stage, weight-for-height z-score, CD4 percent and absolute count and log viral load) were highly correlated with one another, only the single most predictive variable, i.e. weight-for-height z-score, was included in the multivariate models for virological and immunological outcome. Similarly, only one measure of socio-economic status (formal housing, access to water and electricity, access to a refrigerator and employment) was used at a time in each model, i.e. access to water and electricity. Only socio-demographic factors and regimen were included in building the multivariate model of MR adherence ≥ 90% as the sample size did not allow for inclusion of clinical factors as well. P-values for all statistical analyses are reported exactly with no particular cut-off used to define significance.[36]

At the time that the study was designed, few data on paediatric adherence from resource-constrained countries were available on which to base sample size calculations.

The change from donor-funded ART to the government ART program necessitated ending of the study as the government program did not fund adherence monitoring. By this stage the accumulated sample size was sufficient to detect a 50% reduction in proportion with viral suppression in those with MR adherence <90% with 90% power, assuming that 75% of children had MR adherence ≥ 90%.

Results

Medication was returned on at least one occasion for 115/122 (94%) children who commenced ART with the remaining children deceased (n = 6) or lost to follow-up (n = 1) before their first follow-up visit (figure 1). After 1 year, 88 children were alive and remained in care on ART. Table 1 shows the demographic and clinical characteristics and ART drugs prescribed at baseline. Children were young with a median age (IQR) of 37 (16 – 61) months. Although overall socio-economic status was poor with high levels of caregiver unemployment (73%) and informal housing (49%), most caregivers (88%) had at least secondary education and the majority of children (80%) were from households with access to water and electricity.

Annual average MR adherence

A total of 91/115 (79%) children achieved annual average MR adherence ≥ 90% with 73% of these having adherence ≥ 95% (figure 2). Only 9 (8%) children had average adherence for the full year below 80%. These percentages did not change substantially if adherence <90% was assigned for missing returns in children not returning medication on all possible occasions. The number of children remaining in care at each month and the proportion returning medication as requested is shown in figure 3. There was no change in the proportion of children returning medication over time (p = 0.17). Among only those children who remained alive and in care for the entire first year of treatment (excluding those deceased and LFU; n = 88), the proportion with adherence <90% decreased over time with an OR for having low adherence of 0.91 (95% CI: 0.87 – 0.96; p = 0.000) for each additional month (figure 4). Annual average MR adherence <90% was more likely among the 34/115 (30%) child-caregiver pairs who failed to return empty medication containers/unused medication at more than one follow-up visit (OR = 4.97; 95% CI:1.92 – 12.87; p = 0.001).

Relationship between MR adherence and viral/immunological outcomes

Undetectable viral load was achieved in 62/80 (78%) children with annual average MR adherence ≥ 90% compared to 2/8 (25%) of children with lower adherence (OR = 10.3; 95% CI: 1.92 – 55.7; p = 0.005). In univariate analysis, other factors significantly associated with viral suppression were less wasting as reflected in higher weight-for-height z-score, less severe disease (WHO stage 2 or 3 vs WHO stage 4) and being on a non-ritonavir containing regimen (Table 2). Since nutritional status is an important determinant of WHO stage, only weight-for-height z-score and regimen were included in building an adjusted logistic regression model for the relationship between adherence and viral suppression. After adjustment for wasting, regimen was no longer associated with viral load outcome, however adherence ≥ 90% remained an important covariate associated with viral suppression (Adjusted OR = 5.5 [95%CI: 0.8–35.6], p = 0.075). Sensitivity analysis was performed by recalculating average annual adherence for caregiver-child pairs who did not return medication for one or more months by assigning adherence <90% for months in which medication was not returned, and there remained a significant univariate association between MR adherence ≥ 90% and undetectable viral load, and a strong trend towards an association after adjustment for baseline weight-for-height z-score. There was no association between MR adherence in the month or 2 months preceding viral load measurement and viral suppression in either univariate analysis or after adjustment for baseline weight-for-height z-score. Similarly no association was found between the proportion of visits in which caregivers failed to return medication and viral suppression in either univariate or adjusted analyses.

The median (IQR) changes in CD4 percent and absolute count were 10.1% (5.7% – 15.2%) and 393 cells/μl (113 – 654) respectively. There was no association between annual average MR adherence ≥ 90% and either CD4 percent at 1 year, or change from baseline CD4 percent or absolute count over 1 year in either univariate analysis or models adjusted for other determinants of immunological response.

Excess MR Adherence

Using the uncapped annual average MR adherence, 47/115 (40.9%) of children had adherence >100%. This was more common among children taking ritonavir (30/50 [60%]) compared to those on efavirenz (17/65 [26%]; p = 0.000). Adherence >100% was also more common in those 2 years of age or less (28/37 [75.7%]) compared to older children (19/78 [24.4%]; p = 0.000). This age-related difference in excess adherence was maintained after stratifying for ritonavir-based regimen (p = 0.02 and 0.05 for those with ritonavir-based and efavirenz-based regimens respectively).

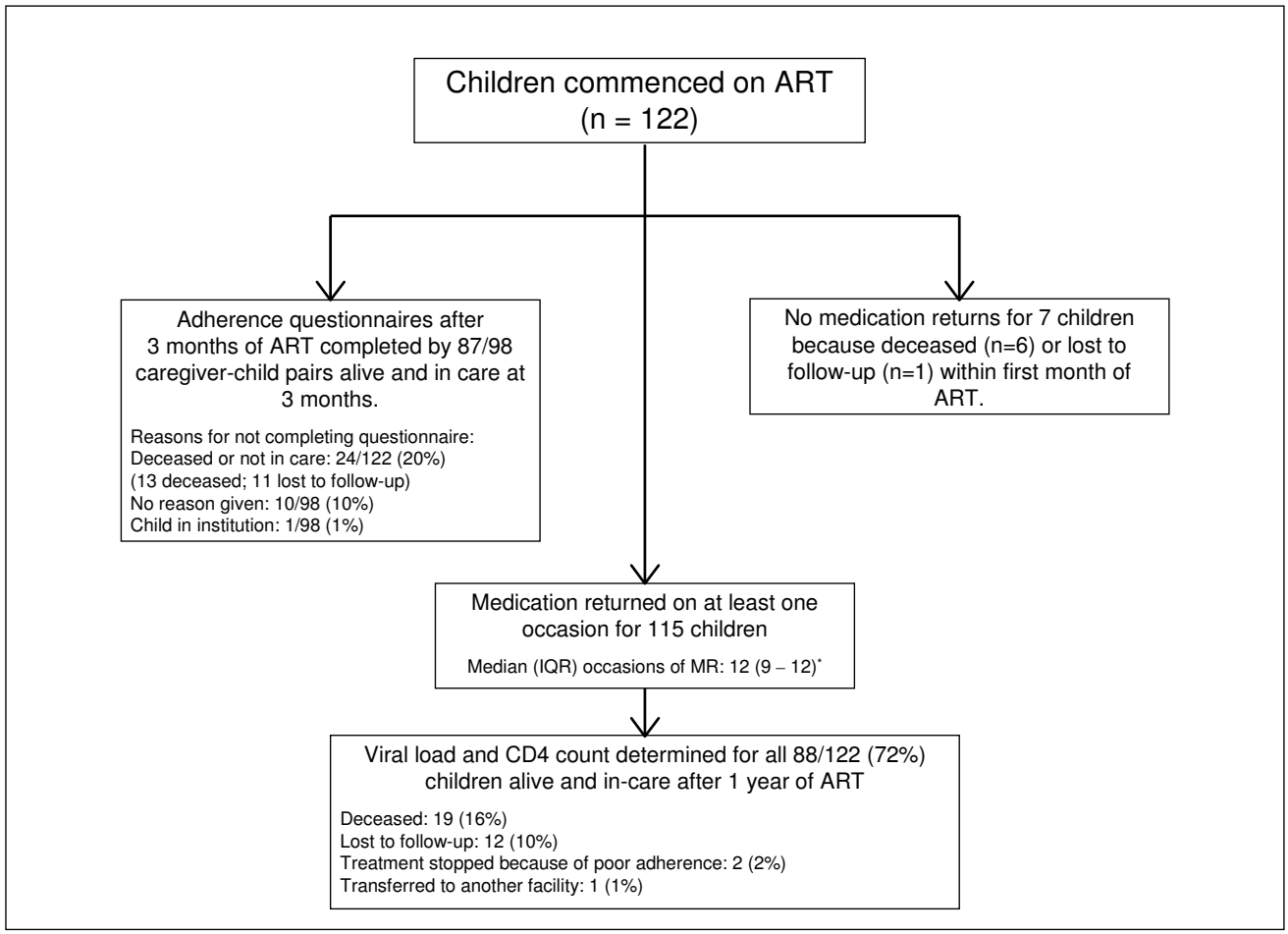
Questionnaire responses

Of 98 children alive and in care after 3 months of ART, 87 (90%) completed adherence questionnaires (figure 1). Annual average MR adherence ≥ 90% was more common in those who completed questionnaires (59/87 [68%] vs 4/11 [36%]; p = 0.051).

Table 1: Social, demographic and clinical characteristics at start of ART according to annual average MR adherence.

Variable	All children (n = 122)	Adherence ≥ 90% (n = 91) (79%)	Adherence<90% (n = 24) (21%)	p-value
Median age (months) (IQR)	37 (16 – 61)	37 (16 – 57)	49 (20 – 72)	0.49*
Gender				
Female (%)	52 (43)	39 (43)	12 (50)	0.53†
WHO stage				
4 (%)	54 (44)	34 (37)	14 (58%)	0.06†
Mean weight-for-age z-score (sd)	-2.02 (1.54)	-1.82 (1.55)	-2.41 (1.37)	0.09‡
Mean height-for-age z-score (sd)	-2.71 (1.36)	-2.66 (1.36)	-2.74 (1.33)	0.78‡
Mean weight-for-height z-score (sd)	-0.56 (1.44)	-0.31 (1.34)	-1.08 (1.42)	0.02‡
Median CD4 percent (IQR)	11.1 (6.9 – 15.0)	11.4 (8.0 – 15.1)	10.1 (4.2 – 14.3)	0.18*
Median CD4 count (IQR)	556 (242 – 908)	592 (273 – 938)	518 (105 – 758)	0.23*
Median Log Viral load (IQR)	5.57 (5.15 – 6.08)	5.44 (5.11 – 6.08)	5.77 (5.30 – 6.06)	0.55*
Primary caregiver				
Mother (%)	107 (88)	79 (87)	21 (88)	0.72§
Not mother (%)	12 (10)	9 (10)	3 (13)	
Unknown (%)	3 (2)	3 (3)	0 (0)	
Median age of caregiver (IQR)	29 (26 – 32)	30 (26 – 32)	28 (25 – 35)	0.58*
Father provides financial support				
Yes (%)	48 (39)	37 (41)	9 (38)	0.8†
No (%)	70 (57)	51 (56)	14 (58)	
Unknown (%)	4 (3)	3 (3)	1 (4)	
Caregiver has secondary education				
Yes (%)	107 (88)	83 (91)	18 (75)	0.03†
No (%)	11 (9)	6 (7)	5 (21)	
Unknown (%)	4 (3)	2 (2)	1 (4)	
Caregiver employed				
Yes (%)	27 (22)	23 (25)	4 (17)	0.37†
No (%)	89 (73)	64 (70)	19 (79)	
Unknown (%)	6 (5)	4 (4)	1 (4)	
Caregiver/child receives social grant				
Yes (%)	69 (57)	55 (60)	11 (46)	0.16†
No (%)	51 (42)	34 (37)	13 (54)	
Unknown (%)	2 (2)	2 (2)	0 (0)	
Formal housing				
Yes (%)	62 (51)	50 (55)	8 (33)	0.06†
No (%)	60 (49)	41 (45)	16 (67)	
Access to water and electricity				
Yes (%)	97 (80)	76 (84)	15 (63)	0.024†
No (%)	25 (20)	15 (16)	9 (38)	
Access to working refrigerator				
Yes (%)	85 (70)	66 (73)	12 (50)	0.036†
No (%)	37 (30)	15 (16)	12 (50)	
Medication				
d4T (%)	110 (90)	81 (89)	22 (92)	1.00*
AZT (%)	11 (9)	8 (9)	3 (13)	0.70*
3TC (%)	117 (96)	88 (97)	22 (92)	0.28*
ddI (%)	4 (3)	3 (3)	1 (4)	1.00*
Efavirenz (%)	67(55)	55 (60)	10 (42)	0.08†
Ritonavir (%)	55 (45)	36 (40)	14 (58)	0.10†

*Wilcoxon rank sum test
‡Student's t-test
†Chi^2 test
§Fisher's exact test



*Medication was returned on all possible occasions for 50% of children

Figure 1
Profile of study.

Reported missed doses

NFA (missing ≥ 1 dose in the previous 3 days) was present in 12/87 (13.8%) children, and was more common in those whose MR adherence for that month was <90% (7/22 [31.8%]) vs 5/62 [8.1%]; p = 0.006). Nevertheless, the sensitivity of NFA for poor MR adherence in the preceding month was only 31.8% (95% CI: 10.7% – 53.0%) and agreement between the two measures was only slightly better than that expected by chance (κ = 0.278; p = 0.003). There was no association between NFA and viral response at 1 year (p = 0.965). Although 38/87 (43.7%) of caregivers were unable to describe how to give their child's ART regimen exactly, this was not associated with either NFA or MR adherence <90% (p = 0.88 and p = 0.68 respectively).

Experience with giving medication

A notable number of caregivers (33/87 [38.4%]) experienced problems with giving ART medication. Poor palatability of medication was the most common problem (21.8% of caregivers), with 68% of these being attributed to ritonavir. Change in daily routine was a problem for 12.6% of caregivers. Experiencing problems with giving medication did not affect reported (OR = 2.13; 95%CI: 0.59 – 7.65; p = 0.32) or MR adherence (OR = 0.61; 95%CI: 0.22 – 1.65; p = 0.32) in the month in which problems were reported, but was associated with annual average MR adherence <90% (OR = 3.07; 95% CI: 0.91 – 10.38; p = 0.06).

Most (65/87 [74.7%]) caregivers used at least one method to assist with remembering and giving medication. The most commonly used aids were activities of daily living reminders (35 [40%]) and treatment partners (23 [26%]). While the vast majority of caregivers (81 [93%]) believed that ART medication was improving their child's health, a significant number (24 [28%]) were unsure or believed that their children would not deteriorate if ART was

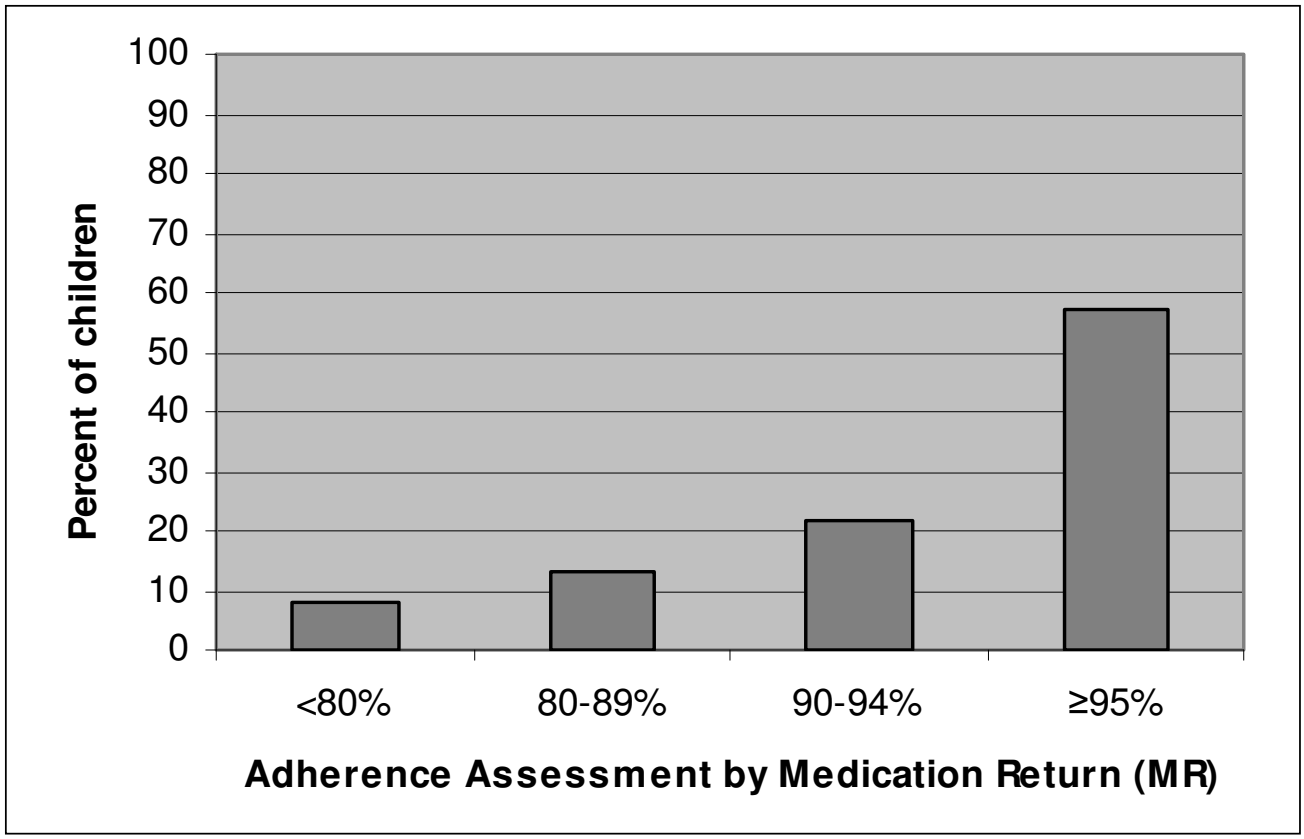


Figure 2
Annual average MR adherence (n = 115).

stopped. Caregiver beliefs did not influence adherence by any measure.

Determinants of annual average MR adherence ≥ 90%

Socio-demographic variables most strongly associated with annual average MR adherence ≥ 90% on univariate analysis were caregivers having secondary education and household access to water and electricity as well as a refrigerator (tables 1 and 3). Having secondary education was not significantly associated with any of the indicators of socio-economic status. Being on an efavirenz-based regimen was less strongly associated with good adherence. Secondary education of the caregiver and household access to water and electricity were both independent socio-demographic predictors of annual MR adherence ≥ 90%, while taking ritonavir was negatively associated with MR adherence ≥ 90%.

Discussion

This study extends to infants and young children the finding that good adherence to ART in Africa is achievable with nearly 80% of children obtaining average MR adherence ≥ 90% over the first year of ART. [16,25,26,28] This is at least as good as pediatric adherence in rich countries.[13,17-22] This excellent adherence occurred despite nearly 40% of caregivers experiencing subjective difficulty with administering medication. Secondary education, access to water and electricity and a non-ritonavir based regimen were all independently associated with better adherence. This study demonstrates that although clinic-based medication measures may not be as sensitive as unannounced home-based measures or MEMS monitoring to detect poor adherence, they are still strongly predictive of virologic response. Annual average MR adherence ≥ 90% was associated with a greater than 5 fold increased likelihood of suppressing viral load at the end of the year.

The excellent adherence seen in our study may, however, not be representative of current pediatric adherence in Africa as ART is scaled up. These were the first children to receive ART at our tertiary care institution and many were well-known to the HIV service as adherent with other medications and clinic visits. In addition, the social criteria used to determine ART eligibility may have further selected those patients more likely to be adherent. Furthermore, treatment was donor-funded in the context of

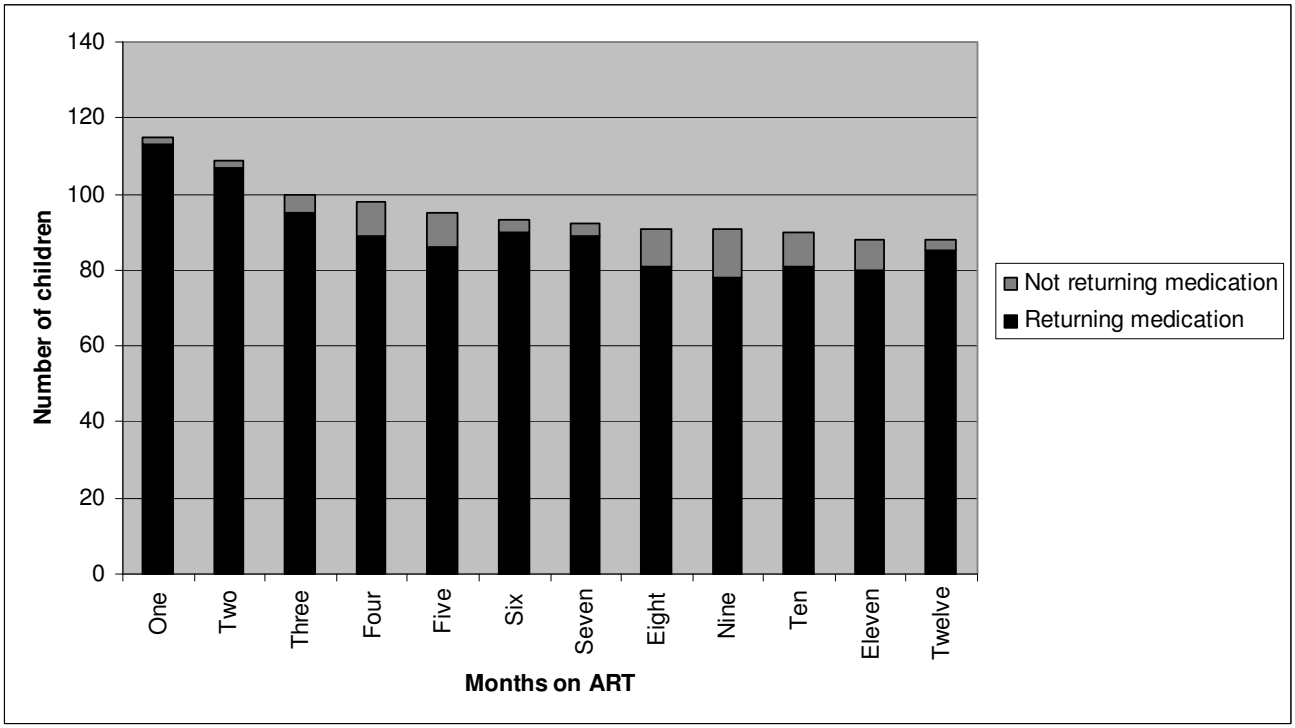


Figure 3
Number of children in care at the end of each month on ART. Total number of children in care at the end of each month divided into those returning and not returning medication

no access to ART through government health services so caregivers may have felt that ART was a privilege. Moreover, regular adherence monitoring may have enhanced adherence. While the halving of the proportion of children with MR adherence <90% during the year supports this, it is a problem inherent to all adherence studies. In addition, the actual estimate of adherence may be inflated by use of clinic-based medication measures. The finding by Muller et al.[29] of much lower adherence using MEMS caps in a recent post-national ART roll-out study in a similar setting to ours supports the likelihood of both particularly good adherence in our cohort, and of adherence being over-estimated by our method of measurement. Nevertheless, the strong association with viral suppression in our study indicates at least reasonable accuracy of adherence measurement.

In contrast, reported NFA showed no relationship to viral outcome and was only 32% sensitive for MR adherence <90%. While the failure to find an association with viral suppression may well be due to the fact that reported adherence was only measured once long before viral load measurement, the tendency for caregivers and patients to over-estimate adherence is well established.[15,23,28,29,32] In our study, this may have been exacerbated by interviews being conducted by clinicians to whom caregivers might be reluctant to admit to missing doses, particularly in the context of limited access to ART. This, however, reflects clinical practice.[15], and any attempts to develop a screening tool for poor adherence in busy roll-out clinics must take into account under-reporting of non-adherence to clinicians. In this study, the additional measuring of adherence by medication return should have, at least in part, mitigated against under-reporting.

Interestingly we found no association between MR adherence in the month or 2 months immediately prior to viral load measurement, in contrast to the strong association with average MR adherence over the whole year. Other studies have found strong associations between short-term adherence and viral suppression immediately thereafter. [12,29] Having a single viral load measurement only after a full year on treatment made it impossible to examine the effect of short-term fluctuations in adherence on viral outcome. The small sample in this study may also have reduced its power to show such an association particularly as a far smaller number of children than expected had poor adherence. In addition, the sample size limited the number of predictor variables that could be used in

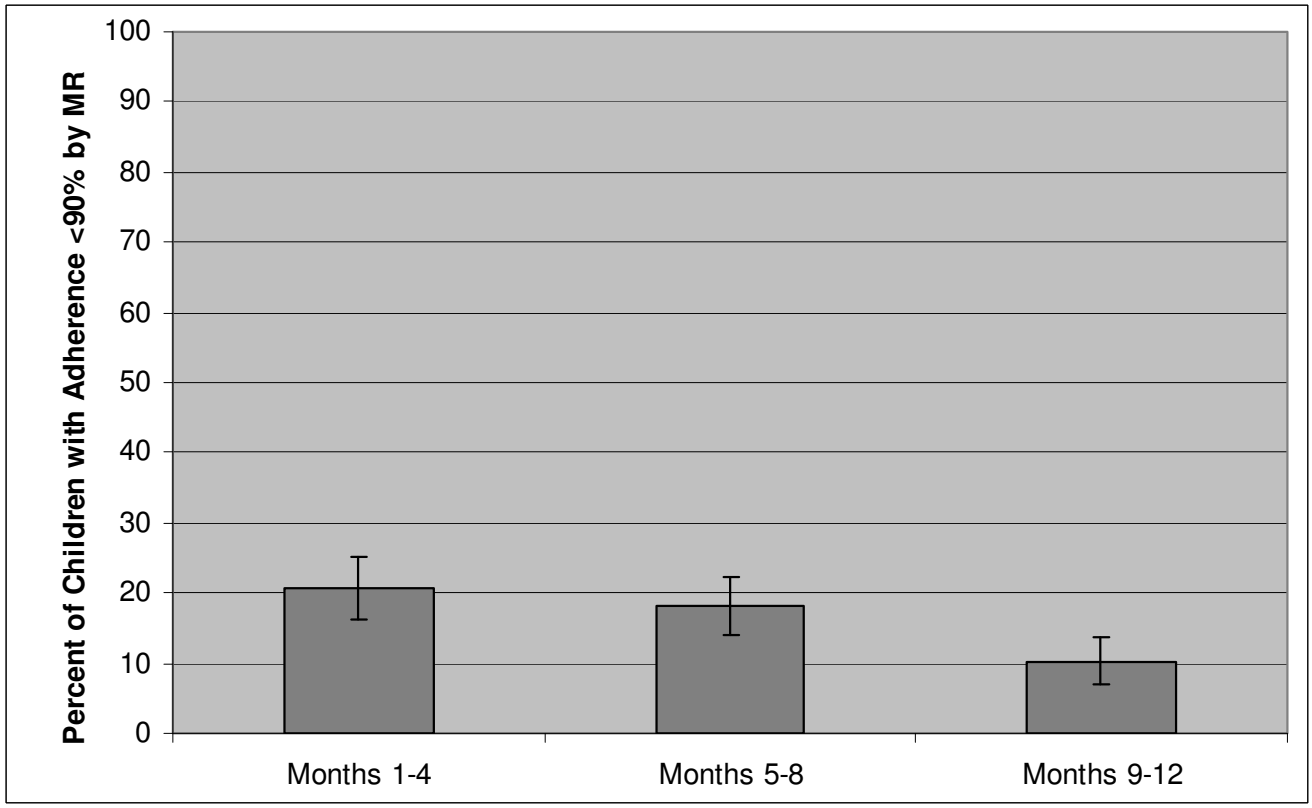


Figure 4
Changes in proportion with MR adherence <90% during the first year on ART. Only children who remained alive and in care for entire first year of treatment (excludes children deceased or LFU; n = 88).

analytic models. We were only able to include a single indicator of disease severity in the model of viral suppression and only able to include socio-demographic and regimen factors as predictors of MR adherence ≥ 90%.

It is notable that nearly 40% of caregivers experienced problems with giving ART, and that this adversely affected adherence over the whole year. Poor palatability of medication was the most common problem reported, especially in those taking ritonavir. This problem is unique to infants and very young children taking liquid formulations of drugs, and concurs with international studies.[18,22] A limitation of our study is that drug formulation was not recorded so its effect on adherence

Table 2: Univariate and multivariate factors associated with undetectable viral load (n = 88)

Variable	Unadjusted OR	95%CI	p-value	Adjusted OR	95%CI	p-value
Female gender	0.91	0.36 – 2.35	0.86	†		
Age at treatment start (months)	1.00	0.99 – 1.01	0.81	†		
WHO stage 2&3 (vs WHO stage 4)	2.80	1.07 – 7.35	0.04	*		
Weight-for-age z-score	1.29	0.94 – 1.77	0.12	*		
Height-for-age z-score	1.07	0.74 – 1.54	0.71	*		
Weight-for-height z-score	1.94	1.27 – 2.96	0.002	1.8	1.15 – 2.80	0.01
CD4 percent	1.04	0.97 – 1.12	0.27	*		
CD4 absolute (cells/l)	1.44	0.54 – 3.84	0.47	*		
Log viral load	0.87	0.48 – 1.60	0.66	*		
Ritonavir-containing regimen	0.33	0.13 – 0.87	0.03	†		
Annual average MR adherence ≥ 90%	10.30	1.92 – 55.67	0.005	5.48	0.84 – 35.58	0.075

*Not included in building multivariate model
†Not significantly associated with viral suppression after adjustment for weight-for-height z-score

Table 3: Factors associated with annual average MR adherence ≥ 90%. (n = 115)

Variable	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Access to water and electricity	3.04	1.12 – 8.22	0.028	2.65	0.93 – 7.55	0.069
Formal housing	2.44	0.95 – 6.27	0.064	*		
Access to working refrigerator	2.64	1.04 – 6.65	0.039	*		
Secondary education (>Std 5/Grade 7)	3.84	1.06 – 13.98	0.041	4.49	1.10 – 18.24	0.035
Taking ritonavir	0.44	0.18 – 1.11	0.084	0.37	0.13 – 1.02	0.054

*Not included in multivariate model as only one measure of socio-economic status (access to water and electricity) used.

could not be examined. However, the finding that a greater proportion of children under 2 years of age (who would all be taking liquid formulations) had adherence >100% suggests that repeat dosing of syrups/solutions is frequently necessary, placing an additional burden on caregivers.

It is further noteworthy that MR adherence results in the ritonavir group appear paradoxical: taking ritonavir was both negatively associated with (capped) MR adherence ≥ 90%, and positively associated with (uncapped) MR adherence >100%. The excess adherence is explained by frequent need for repeat dosing. However poor adherence in the ritonavir group when measures are capped indicates that there is not always compliance with frequent dosing with an unpalatable drug ultimately impacting negatively on adherence. Indeed the poor adherence in the ritonavir group was attributable to poor adherence to ritonavir alone, with adherence to the other two drugs in the regimen being acceptable (data not shown). Although ritonavir is no longer used as a single third agent in ART regimens, Kaletra® (lopinavir/ritonavir) is also unpalatable and is recommended in the South African national guidelines as part of the first-line regimen in children under 3 years of age.[37] Moreover, drugs other than ritonavir accounted for nearly a third of palatability problems. The need for pediatric-friendly formulations of ART cannot be over-emphasized.

While some studies have suggested that older children are more likely to be non-adherent, we found no relationship between age and adherence.[20,30] However, in our study the median age was young (36 months) with few children approaching adolescence, so its potential negative effect could not be determined. Nevertheless, it should be noted that the age of children commencing ART at our institution has decreased since this initial program, with the majority of children now being less than 2 year old.[8] Our findings may therefore not be applicable to our current patient cohort, and there is a need for further research into adherence in very young infants in Africa.

While previous research in Africa has found little impact of socio-economic status on adherence, our study suggests that better caregiver education and socio-economic status are both strongly independently associated with better adherence. [16,25,27,29] Caregivers with secondary education and those with access to water and electricity are 4.5 times and 2.7 times more likely to have adherence ≥ 90% respectively. The lack of association between caregiver education and any of the indicators of socio-economic status emphasizes that these both impact on adherence and one is not simply a surrogate marker of the other. Compared to adult ART, administering medication to children, particularly infants, is more complex and requires exact measurement of dosages, often to a fraction of a milliliter, and compliance with stringent storage requirements. In addition, unlike adults where dosage remains constant over a long period, dosages for children change frequently due to their rapid growth. Although we did not examine the effect of complex dosages and dosage changes on MR adherence, the positive impact on adherence in children of better education and socio-economic status of their caregivers is not surprising. However, the failure to find an association with caregiver's ability to describe a regimen and adherence suggests that it is the caregiver's overall education that impacts more on treatment adherence than treatment literacy per se.

Conclusion

This study demonstrates the potential for caregivers of African young children to achieve adherence comparable with that of wealthier countries. The association between MR adherence and viral response attests to the value of a relatively simple low technology tool for measuring adherence i.e. clinic-based medication return for detecting lapses in adherence. Nevertheless, repeated measurements of medication returned, particularly of syrups/solutions, are not feasible in most large program scale-up settings and the poor sensitivity of low reported adherence for low MR adherence highlights the need to develop practical easy-to-use reliable screening tools to detect children in whom more intensive adherence monitoring is indicated. [30] The negative impact of problems experienced with giving ART, unpalatable drugs, poor caregiver

education and socio-economic status on adherence in this study underscores the need for more pediatric-friendly drug formulations as well as the importance of supporting caregivers in providing ART to children.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MD conceived of the study, participated in its design and co-ordination, performed statistical analysis and drafted the manuscript. BE participated in the design and co-ordination of the study and advised on analysis. AB provided advice on statistical analysis. JN participated in the design and co-ordination of the study. TF carried out all medication measurements. All authors read and approved the final manuscript.

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PART D: SUPPORTING DOCUMENTS

ANNEXURE A: ABRIDGED STUDY PROTOCOL FOR ANTIRETROVIRAL THERAPY FOR A COHORT OF HIV-INFECTED CHILDREN AND THEIR INFECTED PARENTS AT RED CROSS CHILDREN'S HOSPITAL

Antiretroviral therapy: guidelines for the treatment of a cohort of HIV-infected children and their infected parents at Red Cross Children's Hospital

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BACKGROUND

In the absence of antiretroviral therapy the median survival of HIV-infected children in Cape Town is 34 months. Risk for death is significantly associated with an age of less than 6 months and CDC category C diseases at diagnosis.[1] The efficacy and safety of antiretroviral therapy has been demonstrated in children, adolescents and adults. Current guidelines for treating children recommend combination therapy that includes protease inhibitors (PIs).[2,3] The benefits of PI-combination regimens include decreased risk for death, improved growth, better immunological reconstruction, reduction in infectious complications and significant reduction in the progression of the disease to AIDS.[4-7]

The rate of immunological reconstitution differs in children and adults. In children there is early and progressive recovery of naïve CD4+ T-cells but only a small rise memory CD4+ cells. Significantly higher rates of naïve, memory and total CD4+ cells are observed in children less than 3 years of age. These observations suggest that the pattern of CD4+ T-cell regeneration during HAART is thymus-dependant.[8,9] In adults the repopulation of CD4+ T-cells is a biphasic process. Initially, memory CD4+ T-cells increase rapidly within 3 weeks of commencing antiretroviral therapy. This response is probably due to redistribution of CD4+ cells from lymphoid tissue to the peripheral bloodstream. Thereafter memory CD4+ cells remain relatively stable. Naïve CD4+ T-cells by contrast increase gradually but slowly.[10,11]

Efficacy and adherence are important considerations in the management of children on antiretroviral therapy. A smaller proportion of children receiving PI-combination regimens experience suppression of plasma HIV RNA levels below the limits of detection, in comparison to adults. Early studies showed that only 25 to 40% of children receiving these regimens experience suppression of plasma HIV RNA levels below the limit of detection compared with 43 to 75% of adults[12] More recent reports indicate improved efficacy. For example, a open-labelled study of 32 children treated with indinavir or nelfinavir plus zidovudine and lamivudine, showed that after 96 weeks of therapy 69% and 50% of children had achieved viral loads less than 500 and 40 copies / mL, respectively.[13] Four-drug regimens may be superior for controlling viral replication in paediatric HIV infection.[14]

A high level of adherence is needed for virologic success. Adherence is generally lower in children. In one study only 58% of HIV-infected children were able to achieve satisfactory adherence.[15] Factors contributing to lower adherence include difficulty with drug administration because of the complexity of the combination regimens, lack of palatability of liquid formulations and high numbers of tablets/capsules and dosing frequency. Adherence can be improved if regimens are simplified, with ongoing education and by tailoring regimens to the families' schedules. Where administration of medication is particularly problematic, administration via a gastrostomy tube has proven to be safe and effective.[12] Experience with adult South Africans indicate that socio-economic status does not influence adherence.[16]

Red Cross Children's Hospital is one of several hospitals in Cape Town, associated with the University of Cape's Faculty of Health Sciences. The hospital provides care for children with a wide range of tertiary paediatric and paediatric surgical problems, is involved in training undergraduate medical students, specialist paediatricians and paediatric surgeons, and has a number of research programmes in paediatrics and child health. HIV infection is currently the dominant health problem. Between 25 and 30 % of children who are admitted to the hospital's medical wards are HIV-infected. Approximately 23% of all deaths at the hospital

are currently related to HIV infection.[17] A dedicate Infectious Diseases Ambulatory service cares for between 400 and 450 HIV-infected children and their immediate families. Five paediatricians, 2 medical officers (1 exclusively involved with the care of infected parents), 2 nurses, 1 social worker, 1 oral hygienist and 2-3 volunteer counsellors staff the clinic. Care includes cotrimoxazole prophylaxis, treatment of minor infections, nutritional and micronutrient supplementation, and screening for and treatment of children with tuberculosis. Antiretroviral therapy is not administered routinely, but twelve children with access to private funding, are being managed with either dual or triple combinations. Parents receive medical care, and have access to individual and group counselling and educational sessions.

ANITRETROVIRAL TREATMENT PROGRAMME

The major antiretroviral treatment goals for HIV-infected children include the promotion or restoration of normal growth and development, prevention of complicating opportunistic infections and cancers, improved quality of life and prolonged survival.

The principle objective of this treatment programme is to extend access to antiretroviral therapy, of as many children and their parents as is possible.

Secondary objectives include:-

- Adapting existing treatment protocols to local circumstances
- Evaluating effectiveness and adherence locally
- Developing an educational programme on antiretroviral therapy in children and their families for health care workers
- Undertaking a cost benefit analysis of the programme
- Developing parallel research projects around issues such as immunological reconstitution and psychosocial aspects of HIV-infected households.

The Infectious Diseases service at Red Cross Children's Hospital has the facilities, personal and experience to initiate this programme and to conduct relevant operational research.

Selection of children

At present, limited resources preclude the treatment of all children in whom antiretroviral therapy is indicated. Therefore, children will be included in the treatment cohort on the basis clinical, immunological, and selective social criteria. The selection approach is modelled on the European treatment guidelines.[2] Recent research supports delaying the introduction of antiretroviral therapy until advanced disease is present, as highly active antiretroviral therapy has the greatest effect on immune reconstitution when initiated in children with the greatest immunosuppression. The effect of therapy on viral load is not influenced by the immunological status at the time of starting HAART.[18] The social guidelines will be revised and liberalised as circumstances improve, especially increased funding for the project.

Clinical and immunological criteria2

- Clinical stage C or immunological stage 3 (Appendix 1).[19]
- Consider ART if clinical stage B or CD4+ count < 20% or high viral load (>10^6 copies / mL if age < 1 year, and > 10^5 copies / mL if age > 1 year).

Social criteria

- Parent / guardian prepared to commit to long-term antiretroviral therapy
- Parent / guardian having a permanent address in Cape Town for longer than 3 months
- Parent / guardian prepared to complete a detailed questionnaire and serial evaluations
- Parent / guardian prepared to comply with adherence monitoring
- Parent with HIV infection prepared to receive antiretroviral therapy, if indicated
- Child attending the infectious disease clinic regularly, at least the last 3 appointments
- Child taking his / her medication regularly

Exclusion criteria

- Stage N or A disease, and CD4+ count > 20%
- Child currently on antiretroviral therapy
- Parent / guardian not prepared to commit to long-term antiretroviral therapy
- Parent / guardian not having a permanent address in Cape Town for longer than 3 months
- Parent / guardian not prepared to complete a detailed questionnaire and serial evaluations
- Parent / guardian not prepared to comply with adherence monitoring
- Parent with HIV infection not prepared to receive antiretroviral therapy, if indicated
- Child not attending the infectious disease clinic regularly (evaluate at least the last 3 appointments)
- Child not taking his / her medication regularly

Approach to selecting patients

1. Children selected at the infectious disease clinic on the basis of their clinical staging i.e. clinical category C or B (Appendix 1).
2. Caregivers informed of the programme.
3. Caregivers complete a screening questionnaire (Appendix 2).
4. If satisfactory, an initial CD4+ count to be done.
5. All information including a summary of the medical history will be reviewed by a panel of staff members attached to the clinic.
6. The decision of the panel will be discussed with the caregiver within 2 weeks.
7. If a child is accepted onto the programme further information about the programme to be given and consent for antiretroviral therapy to be taken (Appendix 3).
8. The instructions in Appendix 4 should be followed. These include completing a detailed assessment and baseline bloods (Appendix 5), and a neurodevelopmental assessment (Appendix 6). Further information about the programme should be given.
9. Antiretroviral therapy commenced as soon as possible.
10. Antiretroviral therapy will be managed according to established guidelines (see below).

First line therapy for children

The initial regimen should achieve an undetectable viral load in many children, exert a sustained clinical effect and minimise the emergence of drug resistance. To ensure that the programme reaches many children the relative costs of individual drugs were considered. First-line therapy will include two nucleoside reverse transcriptase inhibitors (NRTIs) [one thymidine analogue and one non-thymidine analogue], and a protease inhibitor (PI). The first line therapy may be modified as more funding accrues.

First line antiretroviral regimens[d]	
d4T or AZT plus 3TC or ddI plus Ritonavir or [Lopinavir and ritonavir (Kaletra®)]	Preferred regimen: AZT/3TC/Kaletra Current regimen based on cost considerations: d4T / 3TC[a] plus ritonavir[b]
d4T plus ddI or 3TC plus EFV[c]	Consider as alternative if > 3 years or > 10 kg

[a] Although AZT/3TC combination is regarded as the first line NTRI therapy, cost currently precludes use of this combination. It is easier to administer d4T/3TC than d4T/ddI in young children

[b] Ritonavir suspension is currently the least expensive paediatric PI formulation in South Africa. Its major disadvantage is its taste. Palatability may be improved by coating the child's mouth with peanut butter before administration, mixing the suspension with cold milk, juice, jelly, honey, ice cream, yogurt or chocolate milkshake, or eating salty food (e.g. potato chips or pickles) or chewing gum after taking a dose of the suspension. Some of these measures have been used successfully in South Africa. Unpredictable drug levels in children under the age of 2 years[20] can be somewhat overcome by employing a higher therapeutic dose of 450 mg/m^2. Alternatively lopinavir / ritonavir (Kaletra®) may be considered. There is limited data on the use of NNRTIs in young children with high viral loads. Sine mid-2001 nevirapine has been used in the Western Cape mother-to-child-transmission intervention programme. The K103N resistance mutation has been reported after short-course administration of nevirapine in MTCT intervention programmes[21]. This limits the use of NNRTIs in children recently exposed to nevirapine.

[c] Efavirenz may be an effective alternative in older children, particularly as the median viral load is lower and the improved palatability should influence adherence positively.

[d] Both regimens are compatible with concurrent antituberculosis therapy containing rifampicin.

Individual drugs

STAVUDINE (D4T)[3,20]

Dosage

Paediatric dose: 1 mg per kg body weight every 12 hours (up to 30 kg) Adolescent / adult dose: body weight ≥ 60 kg: 40 mg twice daily; body weight < 60 kg: 30 mg twice daily

Major toxicities

More common: headache, gastrointestinal disturbances, skin rashes
Less common: peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.
Rare: increased liver enzymes

Drug interactions

Should not be administered in combination with AZT

Special instructions

Can be administered with food
Oral solution must be kept refrigerated

LAMIVUDINE (3TC)[3,20]

Dosage

Paediatric dose: 4 mg per kg body weight twice daily
Adolescent / adult dose: body weight ≥ 50 kg: 150 mg twice daily; body weight < 50 kg: 2 mg per kg twice daily

Major toxicities

More common: headache, fatigue, nausea, diarrhoea, skin rash, abdominal pain
Less common: pancreatitis, peripheral neuropathy, decreased neutrophil count, increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Special instructions

Can be administered with food
Oral solutions may be stored at room temperature

DIDANOSINE (DDI)3,20

Dosage

Paediatric dose: In combination with other antiretrovirals: 90 mg/m2 every 12 hours.
Adolescent / adult dose: body weight ≥ 60 kg: 200 mg twice daily. Body weight < 60 kg: 125 mg twice daily.

Major toxicities
More common: diarrhoea, abdominal pain, nausea, vomiting
Less common: peripheral neuropathy (dose related), electrolyte disturbances and hyperuricaemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.
Rare: pancreatitis, increased liver enzymes, retinal depigmentation.

Special instructions
Food decreases absorption; administer ddI on an empty stomach (one hour before or two hours after a meal).
Oral solution: keep refrigerated; admixture stable for 30 days.

ZIDOVUDINE (AZT)[3,20]

Dosage
Paediatric usual dose: 160 mg/m^2 every eight hours
Adolescent / adult dose: 200 mg three times a day or 300 mg twice daily.

Major toxicities
More common: haematologic toxicity, including granulocytopaenia and anaemia, headache
Less common: myopathy, myositis, liver toxicity
Unusual: lactic acidosis and sever hepatomegaly with steatosis, including fatal cases have been reported

Special instructions
Can be administered with food
Decrease dosage in patients with severe renal failure
Reduced dosage may be indicated in patients with substantial hepatic dysfunction

RITONAVIR (RIT)[3,20]

Dosage
Paediatric dose: 400 – 450 mg/m^2 every 12 hours. To minimise nausea and vomiting, commence therapy at 250 mg/m^2 every 12 hours and increase stepwise to full dose over 5 days as tolerated.
Adolescent / adult dose: 600 mg twice daily. To minimise nausea and vomiting, commence at 300 mg twice daily and increase stepwise to full dose over 5 days as tolerated.

Major toxicities
More common: nausea, vomiting, diarrhoea, headache, abdominal pain, anorexia
Less common: circumoral parathesis, increased liver enzymes
Rare: spontaneous bleeding in haemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycaemia, ketoacidotis, diabetes, and hepatitis

Special instructions
Administration with food increases absorption
Oral solution should be refrigerated
To improve tolerance: mix oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream. Coat the mouth with peanut butter before administration.

LOPINAVIR / RITONAVIR (KALETRA®)

Dosage
Paediatric dose:

Six months to 12 years of age (without nevirapine of efavirenz)	
7 to < 15 kg	12 mg per kg lopinavir / 3 mg per kg ritonavir twice daily with food
15 to 50 kg	10 mg per kg lopinavir / 2.5 mg per kg ritonavir twice daily with food
> 50 kg	400 mg lopinavir / 100 mg ritonavir (three capsules or 5 mL) twice daily with food (same as adult dose)

OR

230 mg per m^2 lopinavir / 57.5 mg per m^2 ritonavir twice daily with food, up to a maximum of 400 mg lopinavir / 100 mg ritonavir

Adolescent / adult dose: 400 mg lopinavir / 100 mg ritonavir (three capsules or 5 ml) twice daily with food.

Major toxicities
More common: diarrhoea, headache, asthenia, nausea and vomiting. Increased in blood lipids (cholesterol and triglycerides), and rash in patients on Kaletra and other antiretroviral drugs.
Rare: Spontaneous bleeding in haemophiliacs, pancreatitis, hyperglycaemia, ketoacidosis, diabetes, hepatitis

Drug interactions
Lopinavir / ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.
Efavirenz and nevirapine induce the metabolism of lopinavir and decrease plasma concentrations. A dose increase of lopinavir / ritonavir is recommended.

EFAVIRENZ (EFV)[3,20]

Dosage
Paediatric dose: Administered once daily - body weight 10 – 15 kg: 200 mg; 15 – 20 kg: 250 mg; 20 – 25 kg: 300 mg; 25 – 32.5 kg: 350 mg; 32.5 – 40 kg: 400 mg; > 40 kg: 600 mg
Adolescent / adult dose: 600 mg once daily

Major toxicities
More common: skin rash, CNS problems primarily in adults (somnolence, insomnia, abnormal dreams, confusion, impaired concentration, agitation. Hallucinations, euphoria), increased liver enzymes

Special instructions
Efavirenz can be taken with or without food. Bedtime dosing is recommended.
Capsules may be opened but the granules have peppery taste

Monitoring (Appendix 4)

1. Laboratory

Viral load:	Baseline then yearly Store EDTA plasma (250µl x 2 aliquots) in between i.e. 6mo, 18mo, etc.
CD4+ count:	Baseline and 6-monthly
FBC:	Baseline, 1 month, 3 month, then 3- to 6-monthly
LFTs:	Baseline, 1 month, 3 months, then 3- to 6-monthly
Fasting lipids:	Baseline, then 6- to 12-monthly
Amylase:	6-monthly
Fasting glucose:	Baseline and 6-monthly
Vitamin A:	Baseline and 1 year
Plasma:	Store baseline heparinised plasma (5 aliquots plus a balance tube)

2. Clinical
Follow-up appointments: 2 weeks, 1 month, monthly until 6 months, then 1 to 3 monthly

At each visit the datasheet should be completed (Appendix 7). The clinical team will review datasheets and clinical progress of each child at regular meetings. At yearly intervals a detailed evaluation will be completed (Appendix 12).

3. Adherence
All unused medication must be brought to each clinic visit. Adherence will be monitored by checking quantities of used / unused medication at each visit. An adherence questionnaire will be completed periodically (Appendix 8).

Adverse events[22]

Adverse events will be managed according to guidelines established by the United States Public Health Service and the Infectious Diseases Society of America.[22] The severity of adverse events have been graded according to an internationally accepted system (Appendix 9).

Principles of managing adverse events

1. Try to establish whether the adverse event is due to antiretroviral agents, or other medication.

2. Continue therapy in the presence of non-life-threatening toxicities. Attempts should be made to continue antiretroviral therapy at effective doses except in the presence of severe (grade 4) or life-threatening toxicities, in which circumstances therapy should be stopped. Severe and possibly rapidly fatal complications including pancreatitis, hepatic failure or severe skin rashes including Stevens-Johnson syndrome require discontinuation of the most suspect medication and often, discontinuation of all medication temporarily. Lower-grade toxicities (grades 1 and 2) should prompt increased and more frequent observation, monitoring and evaluation.
3. If there is a need to discontinue antiretroviral therapy for an extended period, it is advisable to discontinue all antiretrovirals rather than continuing with one or two agents alone.

All severe adverse (grade 4) or life-threatening events should be documented (Appendix 10).

Antiretroviral therapy and anti-tuberculous therapy[23-25]

Many patients in sub-Saharan Africa who are candidates for antiretroviral therapy will have active tuberculosis. Tuberculosis is a leading cause of death among HIV-infected individuals. Because of the risk of drug interactions between the PI class of antiretrovirals and rifampicin (in general, serum protease inhibitor levels are lowered substantially and rifampicin levels increased 2 – 3 times the usual concentration), concerns have been raised about the optimal therapy for both tuberculosis and HIV infection. An alternative to rifampicin is rifabutin. This drug is not readily obtainable locally and is expensive. Important treatment issues to address in patients co-infected with tuberculosis and HIV infection and treated with rifampicin-based anti-tuberculous treatment regimens are when to start antiretroviral therapy and which drugs to use.

<u>Guiding principles</u>

1. Anti-tuberculous therapy should be commenced as soon as the diagnosis of active tuberculosis is made irrespective of whether a patient is being treated with antiretrovirals.
2. The first-line antiretroviral treatment regimens in this programme are compatible with rifampicin-based anti-tuberculosis regimens.
3. In children on anti-tuberculosis treatment at the time of recruitment to the programme, and who are not at risk of progression of their HIV infection, antiretroviral therapy should be delayed until the intensive phase of anti-tuberculosis therapy in complete (generally the first 2 months of anti-tuberculosis therapy). This simplifies management and minimises toxicity.
4. In children on anti-tuberculosis treatment at the time of recruitment to the programme, and who are at risk of progression of their HIV infection (immunological category III or extrapulmonary tuberculosis), antiretroviral therapy should be started as soon as possible.
5. For children who develop tuberculosis while on antiretroviral therapy, options include:-
    a. Continue antiretroviral therapy if compatible with anti-tuberculosis therapy.
    b. Discontinue all antiretrovirals during the intensive phase of anti-tuberculosis therapy. Reintroduce antiretrovirals during the maintenance phase.

c. If antiretroviral therapy is not compatible with anti-tuberculosis therapy, discontinue all antiretrovirals during the intensive phase of anti-tuberculosis therapy. Recommence antiretroviral therapy during the maintenance phase of therapy and use a non-rifampicin-based regimen during the maintenance phase.

The treatment of tuberculosis and HIV infection together is problematic. The above guidelines may assist in the managing of most patients. However, decisions may be difficult and should be individualised where exceptional clinical circumstances exist.

Pneumocystis Carinii Pneumonitis (PCP) prophylaxis

Children will be managed according to established PCP prophylaxis guidelines.

Summary of guidelines used by the Infectious Diseases Service, Red Cross Children's

1. PCP prophylaxis should be administered to all children born to HIV seropositive mothers, from the age of 4-6 weeks.
2. PCP prophylaxis should be reviewed at the age of 3-4 months if HIV PCR testing is available. Prophylaxis must be continued if the HIV PCR is positive and discontinued if negative. If PCR testing is unavailable or the result indeterminate, then PCP prophylaxis should be continued until the diagnosis of HIV infection has been disproved.
3. Children with category B and C clinical disease should receive lifelong PCP prophylaxis.
4. Children with category A clinical disease may discontinue prophylaxis after 12 months of age. PCP prophylaxis should be reintroduced with disease progreesion.
5. TMP-SMX chemoprophylaxis regimen

Weight (kg)	**Total daily dose**
< 5.0	5 ml^{+}
5.0 - 9.9	7.5 ml^{+}
10.0 - 14.9	10 ml^{+}
15 - 21.9	15 ml^{+} or 1.5 tablets*
≥ 22	20 ml^{+} or 2 tablets*

$^{+}$ Paediatric suspension, *Single-strength TMP-SMX tablets

TMP-SMX should be administered 3 times per week, on alternative days (e.g. Monday, Wednesday, Friday) or on consecutive days (e.g. Monday, Tuesday, Wednesday). Daily TMP-SMX should be administered in 2 divided doses. Where this is impractical, a single dose may be administered.

6. If TMP-SMX cannot be tolerated dapsone or aerosolised pentamidine may be used.

Discontinuation of PCP prophylaxis

For children treated with antiretroviral therapy, PCP prophylaxis can be discontinued when the CD4+ percentage is consistently above 20% (i.e. a CD4+ percentage > 20% on two independent assessments at least 6 months apart). This is the guideline currently used by the Special Infectious Diseases Service, Children's Memorial Hospital, Chicago (R Yogev, personal communication).

Indications for changing antiretroviral therapy[3,23]

Despite a good clinical and immunological response in children on highly active antiretroviral therapy, selection of resistant viral strains is likely to occur in the absence of complete viral suppression. However, many paediatricians delay changing therapy if there is no signs of clinical or immunological progression. Decisions to change antiretroviral therapy will depend on clinical and immunological criteria. Currently, because of limited resources viral load will be performed at baseline and then at yearly intervals. The initial viral load will be used to select initial antiretroviral therapy. Annual viral load evaluations will primarily be used to assess the effectiveness of antiretroviral therapy. If increased funding is obtained viral loads will be determined more frequently (e.g. 6 monthly) and the results used to determine when to change antiretroviral therapy. in the management of the patients.

Clinical considerations

Clinical signs of response to antiretroviral therapy include improvement in growth in children who previously failed to grow, improvement in neurological signs or neurodevelopment, and decreased frequency of infections (bacterial infections, thrush, and / or other opportunistic infections). The following clinical features warrant consideration of a change in antiretroviral therapy.

1. Progressive cognitive and / or developmental deterioration or development of encephalopathy (Appendix 6).
2. Growth failure.
3. Disease progression i.e. advancement from one clinical category to another (Appendix 1).
4. Recurrences of infections such as oral candidiasis refractory to treatment.

Immunological considerations

Before considering changing antiretroviral therapy because of a decline in CD4+ count, a minimum of one repeated measurement of CD4+ values should be obtained at least 1 week after the initial test.

The following immunological features warrant consideration of a change in antiretroviral therapy.

1. A return of CD4+ count / percentage to or below pre-therapy baseline.

2. Immunological deterioration i.e. advancement from one immunologuical category to another (Appendix 1).[19]

Second line therapy

The following general principles should be considered when choosing a new antiretrovoiral regimen in children who have received previous treatment.

1. When therapy is changed because of toxicity or intolerance, agents with different toxicity and side effect profiles should be selected. In the event of drug intolerance, change of a single drug in a multidrug regimen and in certain circumstances, dose reduction are permissible.
2. When changing therapy because of treatment failure, adherence to therapy should be assessed as a potential cause of failure.
3. If the patient is adherent to the regimen, assume the development of resistance and, if possible, change to at least two new antiretroviral agents. The new regimen should include at least three drugs.
4. When considering changing to a new regimen, all other medication should be reviewed for possible drug interactions.
5. When considering changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life should be considered.

Suggested second line antiretroviral regimens	
Failed previous regimen	New regimen
d4T/3TC plus Ritonavir	AZT/ddI plus EFV or NEL
d4T plus 3TC plus EFV	AZT plus ddI plus Ritonavir
d4T plus ddI plus EFV	AZT plus 3TC plus Ritonavir

Treatment of infected parents

(This section has not been included)

CAPACITY BUILDING

For the past two years the Infectious Disease Clinic at Red Cross Children's Hospital has participated in a mentoring programme whereby doctors from community clinics in the Cape Metropolitan Region (estimated population: 3.15 million) attend the clinic over 4-week cycles and learn about the management of HIV-infected children. Doctors at the clinic have for the past 2 years been involved with the 'roll-out' of the mother-to-child-transmission intervention programme of the Western Cape Government, educating nurses, doctors and clinic managers throughout the Western Cape Province about the intervention programme and paediatric HIV infection. The programme is based on short-course nevirapine therapy coupled with the provision of milk powder to babies of HIV-exposed women for the first 6

months of life. It currently covers between 60 and 70% of pregnant women in the province. By the end of 2002 the programme is scheduled to include about 95% of all pregnancies in the province.

There are few doctors employed in state institutions in South Africa with experience of managing HIV-infected people on antiretroviral therapy. Thus one of the medium term objectives of our proposed programme is to create a centre of excellence for the management of HIV-infected children and to use the skills and experience gained from the programme to educate doctors and other health care professionals throughout the province about antiretroviral therapy in children. This will be done through a mentoring system and regular workshops. This should facilitate the establishment of antiretroviral treatment programmes throughout the province, when therapy becomes more accessible.

STATISTICAL CONSIDERATIONS

All data collected as part of this treatment programme will be entered into Epi Info and Access databases anonymously. The data will be analysed using conventional descriptive and comparative statistical methods. Statistical packages that will be used in the analysis includes Epi Info 2000, Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia and Statistica, Statsoft, Inc, Tulsa, OK, USA.

ETHICAL CONSIDERATIONS

The Chief Director and the Medical Superintendent of Red Cross Children's Hospital have given permission for the establishment of this treatment programme. Although ethical approval is not required to initiate antiretroviral treatment, all documents will be forwarded to the Research Ethics Committee, Faculty of Health Sciences, University of Cape Town for approval of the research components of the programme i.e. data collection and analysis.

Parallel research projects dealing with the neurodevelopmental evaluation of children on antiretroviral therapy, immunological reconstitution of children on antiretroviral therapy and detailed psychosocial descriptions of families at different stages of HIV infection including those on effective treatment (antiretroviral therapy) will be submitted separately to the Research Ethics Committee for consideration. These projects are currently under development.

All families who commit themselves to the programme will be asked to complete the consent process.

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APPENDICES

Note: The following appendices have not been included in order to abridge the document:

- Appendix 6: Developmental assessment
- Appendix 9: Grading of adverse drug reactions for children > 3 months of age
- Appendix 10: Severe or life-threatening adverse event report form
- Appendix 11: World Health Organisation guidelines for the diagnosis of pulmonary tuberculosis in children (modified)[29]
- Appendix 13: WHO clinical staging system for HIV infection (adults)
- Appendix 14 – Information brocuhure for people commencing antiretroviral therapy
- Appendix 15: Adherence questionnaire (adults on antiretroviral therapy)

APPENDIX 1: CDC CLINICAL AND IMMUNOLOGICAL CLASSIFICATION FOR CHILDREN WITH HIV INFECTION[19]

Clinical classification

Category N: Not symptomatic

Children who have no symptoms or signs considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

Category A: Mildly symptomatic

Children with two or more of the following features but none of the conditions in category B or C.

Features: lymphadenopathy (at more than two sites); hepatomegaly; splenomegaly; dermatitis; parotitis; recurrent or persistent upper respiratory infection, sinusitis or otits media

Category B: Moderately symptomatic

Anaemia (< 8 gm/dl), neutropaenia (<1000/mm^3), or thrombocytopaenia (< 100 000/mm^3) persisting ≥ 30 days.
Bacterial meningitis, pneumonia, or sepsis (single episode).
Candidiasis, oropharyngeal, persisting (> 2 months) in children > 6 months of age.
Cardiomyopathy.
Cytomegalovirus infection, with onset before 1 month of age.
Diarrhoea, recurrent or chronic.
Hepatitis.
Herpes simplex virus (HSV) stomatitis, recurrent (≥ episodes within 1 year).
HSV bronchitis, pneumonitis, or oesophagitis with onset before the age of 1 year.
Herpes zoster involving at least two distinct episodes or more than one dermatome.
Leiomyosarcoma.
Lymphoid interstitial pneumonitis or pulmonary lymphoid hyperplasia complex.
Nephropathy.
Nocardiosis.
Persistent fever (lasting > 1 month).

Toxoplasmosis, onset before 1 month of age.
Varicella, disseminated (complicated chickenpox).

Category C: Severely symptomatic

Serious bacterial infections, multiple or recurrent.
Candidiasis, oesophageal or pulmonary.
Cryptococcosis, extrapulmonary.
Cryptosporidiosis or isosporiasis with diarrhoea persisting > 1 month.
Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes).
Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or MRI; c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance.
Kaposi's sarcoma.
Lymphoma, primary, in brain.
Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype.
Mycobacterium tuberculosis, disseminated or extrapulmonary.
Mycobacterium avium complex, or *Mycobacterium kansasii*, disseminated.
Pneumocystis carinii pneumonia.
Progressive multifocal leukoencephalopathy
Salmonella (nontyphoid) septicaemia, recurrent.
Toxoplasmosis of the brain with onset at > 1 month.

Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss > 10% of baseline OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g. 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age OR c) < 5th percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhoea (i.e. at least two loose stools per day for ≥ 30 days) OR b) documented fever (for ≥ 30 days, intermittent or constant).

Immunological classification

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

APPENDIX 2: SCREENING QUESTIONNAIRE

Date of completion: _____/_____/_____ (dd/mm/yyyy)

Name of patient:_____

Folder number:_____

Date of birth: _____/_____/_____ (dd/mm/yyyy)

Diagnosis of HIV infection[b]:_____

Clinical classification[c]:_____

Immunological classification[c]:_____

Name of parent or caregiver (if parent is not caregiver):_____

Why are parents not the caregiver?: _____

Address: _____
_____ _____
_____ _____
_____

Contact number:_____

Relation to patient:_____

Is caregiver prepared to commit to long-term antiretroviral therapy:_____

Does caregiver have a permanent address in Cape Town for longer than 3 months:_____

Is caregiver prepared to complete a detailed questionnaire and serial evaluations:_____

Is caregiver prepared to comply with adherence monitoring:_____

Is parent with HIV infection prepared to receive antiretroviral therapy, if indicated:_____

Has child been attending the IDC regularly (at least the last 3 appointments):_____

Is child taking his / her medication regularly: _____

Decision of panel:_____

If accepted onto programme registration number (for data collection):_____

Notes

a) Doctor must present a summary of the clinical history of patient
b) The CDC's paediatric HIV infection diagnosis guidelines will be followed i.e. evidence of HIV exposure and a positive HIV PCR result if age < 18 months and two positive HIV ELISA results if age > 18 months.[19]
c) According to CDC classification system (Appendix 1).[19]

APPENDIX 3: CONSENT PROCEDURE

Antiretroviral therapy for HIV-infected children

Assigned registration number:_____

In rich countries antiretroviral therapy is considered routine treatment for people with HIV infection. Antiretroviral therapy has revolutionised the lives of many HIV-infected adults and children. The benefits to HIV-infected children include decreased risk for death, improved growth and fewer infections such as discharging ears, pneumonia, TB and diarrhoea. Some children who developed HIV infection soon after birth are living to beyond the age of fifteen years and remain healthy, because they are being treated with antiretroviral therapy.

Doctors at the Infectious Diseases Clinic, Red Cross Children's Hospital are involved in establishing a long-term treatment programme for HIV-infected children and their caregivers. This is not a research project but rather one of many responses to the uncontrolled HIV epidemic that has inflicted tremendous suffering on the South African population. The aim of the programme is to provide optimal medical treatment i.e. antiretroviral therapy to as many HIV-infected children and their caregivers as is possible. The success and sustainability of the programme is dependant on the ability to continue to attract local and international funds. As part of the programme we will be documenting the medical progress of the children as well as the problems of treating HIV-infected children with antiretroviral drugs in South Africa. This is important as the information will allow us to adapt the programme to suite the treatment needs of HIV-infected South Africans. All information will be entered into a database and analysed anonymously. This information will be communicated to the academic community at conferences and via publications in peer-review journals. Blood will be collected periodically to monitor the effects of treatment, including CD4+ count, viral load and other immunological markers.

If you decide that your child should not participate in this programme, it will not affect the way we treat your child. S/he will continue to receive the same standard of care that s/he presently experiences.

Consent

I understand the above information as explained to me by:_____**and am prepared to have my child (NAME):**_____**participate in this antiretroviral therapy programme. I understand that strict adherence is needed for continuation of antiretroviral therapy. The programme is dependant on financial donations and a time may come when antiretroviral therapy may be discontinued because of a lack of resources. Should antiretrovirals be discontinued my child will continue to attend the infectious diseases clinic and receive medical treatment.**

NAME: _____

RELATION TO CHILD:_____

SIGNATURE:_____

DATE: ____/____/____ (dd/mm/yyyy)

WITNESSES: _____

_____

BYLAE 3: TOESTEMMINGS PROCEDURE

Anitretroviral therapy for HIV- infected children
Registrasie nommer:_____

In bevoorregde lande is ART ‘n roetine behandeling vir mense wat met die HIV besmet is. ART het die lewens van kinders en grootmense hervorm. Voordele van hierdie behandeling vir kinders wat met die HI Virus besmet is sluit in vermindering van die risiko van vroeer sterfte, verbeterde groei en ontwikkeling plus vermindering van infeksies soos, oor infeksies, long ontsteking, TB en diarree. Somige kinders wat die HIV infeksie ontwikkel gou na geborte, lewe nou tot die ouderdom van 15 jaar en bly gesond omdat hulle met ART behandel is.

Geneeshers by die Besmetlikheid Siektes Klinik by Rooi Kruis Kinder Hospitaal, is betrokke by die ontwikkeling van ‘n lang termyn behandelings program vir kinders wat met HIV besmet is en hul oppassers. Hierdie is nie ‘n narvorsings projek nie maar een van die reaksies tot die onbeheerde HIV epidemie wat Suid Afrika op die oomblik laat ondergaan. Die doel van die program is om gunstige sorg te verskaf, d.i. om ART behandeling vir so veel moontlik HIV besmette kinders en hul oppassers toe te dien. Die sukses van die program is afhanklik van die vermoe om aanhoudend binnelands en buitelandse vondse aan te trek. As deel van hierdie progam sal ons die mediese verloop van al die kinders dokumenteer asook die probleme wat hierdie kinders op die program ondervind. Dit is belangrike informasie en dit sal ons die nodige inligting gee om hierdie program to ontwikkel en die behandeling behoftes aan te pas vir ander HIV besmette kinders in SA. Alle informasie sal op ‘n database ingeskryf word en sal naamloos ontleed word. Hierdie informasie sal versprei word deur die akademiese gemeentskap by konferensies en inskrywings in medise joernale. Bloed sal periodies van kinders geneem word om die uitwerking van die behandeling te monitor insluitend CD4+ telings, virus vrag en ander immun merker.

As u besluit dat u nie u kind in hierdie program will inskryf nie, sal dit nie die huidige manier van sy behandeling beinvloed nie. Hy/Sy sal nog steeds dieselfde hoe standard van sorg kry.

Toestemming

Ek verstaan die bogenoemde informasie soos aan my verduidelik deur_____ en ek is bereid om my kind (naam)_____ in hierdie program te laat deel neem. Ek verstaan dat ek streng moet aankleef soos benodig vir aanhoudende ART behandeling. Hierdie progam is afhanklik van geldelike donasies en daarvoor mag die program skelik stop omdat die donasies nie voorkomend is nie. Sou dit gebeur sal my kind nog steeds die Besmetlikheid Siektes Klinik bywoon en huidige medise behandeling ontvang.

Naam: _____

Verwantskap tot kind: _____

Handtekening: _____

Datum: _____/_____/_____ (dd/mm/yyyy)

Getuie: _____

_____

I-APPENDIX 3: INDLELA YOKUNIKA ISIVUMELWANO

Unyango ngamachiza alwa intsholongwane kaGawulayo (HIV) kubantwana abanayo.
Inombolo yobhaliso enikeziweyo:_____

Kumazwe atyebileyo unyango ngamachiza okulwa intsholongwane kaGawulayo luqatshelwe njengonyango olunokulandelwa ngabantu abosuleleke yile ntsholongwane. Olu nyango ngamachiza seluvuselele ubomi babantu abadala nabantwana abaninzi abosuleleke yile ntsholongwane. Inzuzo kubantwana abanentshlongwane kaGawulayo ibandakanya ukucutha amathuba okusweleka, ukukhula ngokufanelekiyo kunye nokosuleleka okumbalwa zizifo ezinjengokuphuma ubofu ngeendlebe, inyumoniya, isifo sephepha (TB) kunye norhudo. Abantwana abafunyenwe yile ntsholongwane kaGawulayo emva kokuzalwa bayaphila de bagqithe kwiminyaka elishumi elinesihlanu kwaye babe besaphile kakuhle ngokwase mpilweni, kuba benyangwa ngala machiza.

Oogqirha kwiKliniki yezifo ezosulelayo, eRed Cross Children's Hospital bazibandakanye nokumisela inkqubo ende yonyango lwabantwana abanale ntsholongwane kunye nabantu ababakhathalelayo. Olu asilophando oluzakuphela kwangoku koko yenye yeendlela zokusabela kwisihelegu sentsholongwane kaGawulayo engalawulekiyo nethe yalulwamvila lwentlupheko kuluntu lwaseMzantsi Afrika. Iinjongo zale nkqubo kukunika unyango olufikelelekayo, oko kukuthi, ukunika abantwana abanale ntsholongwane nabagcini babo amachiza nonyango olufanelekileyo kangangoko. Impumelelo nokuqhubela phambili kwale nkqubo kuxhomekeke ekukwazini ukutsala abanokunikezela ngemali balapha eMzantsi Afrika nabamazwe ngamazwe. Indima yale nkqubo iyakuba kukwenza amaxwebhu olwazi ngenkqubela phambili yabantwana kunye neengxaki abathi babenazo ekunyangeni abantwana abanale ntsholongwane ngala machiza eMzantsi Afrika. Lo nto ibalulekile njengoko ulwazi luya kusivumela ukuba simisele le nkqubo ukuze unyango luhambelane neemfuno zabantu abanentsholongwane kaGawulayo eMzantsi Afrika. Lonke ulwazi luyakugcinwa kwaye luhlalutywe ngokungasebenzisi gama lamntu. Olu lwazi luyakunikwa i inzululwazi nenkcuba-buchopho ukuba zilusebenzise kwiinkomfa nakupapasho. Igazi liyakumana litsalwa ukujonga ukusebenza kwalamachiza, okubandakanya i-CD4 count, ubuninzi bentsholongwane egazini kunye nezinye iimpawu ezilwa nosuleleko.

Ukuba ugqiba ukuba umntwana wakho angayithabathi inxaxheba kule nkqubo, lo nto ayisayi kuchaphazela indlela ebenyangwa ngayo lo mntwana wakho. Uyakuqhubeka efumana ukhathalelo olufanelekileyo alufumanayo ngoku.

Isivumelwano

Ndiyaluqonda olu lwazi lungentla njengoko lucaciswe ngu:_____ kwaye ndikulungele ukunikezela ngomntwana wam (IGAMA):_____ ukuba athabathe inxaxheba kolu nyango ngamachiza okulwa intsholongwane kaGawulayo. Le nkqubo ixhomekeke kwiimali ezisisipho kwaye lingafika ixesha lokungaqhubekeli phambili ngenxa yemali engekhoyo. Ukuba angangabikho la machiza, ndiyakuqhubekeka ndimsa umntwana wam kwikliniki yezifo ezosulelayo, ukuba afumane unyango.

IGAMA:_____

UZALWANO NOMNTWANA _____

USAYINO:_____

UMHLA:____/____/_____ (umhla/inyanga/unyaka)

AMANGQINA:_____

_____

APPENDIX 4: SUMMARY CLINICAL AND BLOOD COLLECTION INSTRUCTIONS FOR CHILDREN

CLINICAL

- Initial assessment (complete Appendix 5)
- Mantoux testing
  - before enrolling children on treatment programme
  - read horizontal diameter in mm
- Neurodevelopmental follow-up (complete Appendix 6)
  - baseline, and 6 month and 1 year after starting ARV
- Follow-up assessment (complete Appendix 7 at each clinic visit)
  - 2 weeks and 1 month after starting ARV
  - then monthly to 6 months
  - then 1-3 monthly
- Adherence questionnaire (complete Appendix 8)
  - 3, 6 and 12 months after starting ARV
- Detailed yearly evaluation (complete Appendix 12)

BLOOD-TAKING AND LABORATORY ISSUES

1. Viral load: Place 1.5 mL blood into an EDTA tube (Purple top) and mix well
   Sampling: baseline then 6-monthly
   Immunology laboratory:
   Send baseline and yearly samples to virology for viral load
   Store 2 x 250 µL aliquots of EDTA plasma @ -70°C at 6 mo, 18 mo, ..
2. CD4+ count: Place 1.0 mL blood into an EDTA tube (purple top) and mix well
   Sampling: baseline, then 6-monthly
3. FBC + diff: Place 1.0 mL blood into an EDTA tube (purple top) and mix well
   Sampling: baseline, 1 month, 3 months, then 3-6 monthly
4. Chemistry: Place 1.0 mL blood into a heparin tube (green top) and mix well
   - Liver function tests to minimise costs only request
     - total bilirubin
     - conjugated bilirubin if total bilirubin is elevated
     - aspartate transferase (AST)
     - γ-gluteryl transferase (GGT)

     Sampling: baseline, 1 month, 3 months, then 3-6 monthly (yearly samples important)
   - Pancreatic amylase
     Sampling: 6-monthly
5. Fasting lipids: Place 1.5 mL blood into EDTA tube (purple top) and mix well
   Sampling; baseline, then 6 and 12 months
   On a separate chemistry request form write: Attention Professor Marais, Lipid Lab, 5th floor SAMIOT Building, Medical School. Mark: ARV Paediatric study and indicate whether baseline, 6-month or 12-month sample. Request: Fasting lipids (cholesterol, triglycerides and GGE (gradient gel electrophoresis)
6. Vitamin A and RBP: Place 2.5 mL blood into special heparin tube covered with tin foil
   Sampling: baseline and 1 year
   Immunology laboratory
   Prepare aliquots for vitamin A and RBP (500µl and 250µL) and store
7. Vaccine titres: Place 3 ml blood into clotted tube (red top)
   Sampling: baseline and 1 year
   Immunology laboratory
   Save 5 x 300µL aliquots of serum and a balance tube and store at -70°C
7. Fasting blood glucose: 1.0 mL blood in grey top tube
   Sampling: 6-monthly

LABELLING OF SAMPLES

On microbiology form for viral load requests write: **HUSGD - Family clinic** (this will ensure that it is costed to the correct account.
CD4 counts/vitamin A/RBP/vaccine titres write: ARV study, if registration number available please include
For ease of blood taking: do FBC, LFTs and baseline vaccine titres at the same time as screening CD4+ count.

APPENDIX 5: INITIAL ASSESSMENT - PAGE 1

I BIOGRAPHICAL / SOCIAL PROFILE

Registration number (assigned to patient):_____

Date of completion: _____/_____/_____ (dd/mm/yyyy)

PRIMARY CAREGIVER

Mother

Age (years):	Primary caregiver: 1. yes		2. no
HIV status	1. unknown	2. positive	3. negative

Relationship status	1. single	2. partner	3. married	Duration (2/3):
Are you married to the child's father?		1. yes		2. no

Education (level attained):

Are you employed?	1. yes	2. no	Nature of work:

Does the child's father help with money?	1. yes	2. no

Does anyone else help financially?		1. yes	2. no
Who?	1. your parent	2. other family	3. another partner
4. your sibling	5. friend	6. other, specify:	

Do you receive a grant?	1. yes	2. no
Child support grant	Care dependency grant	Disability grant (self)

Is other parent living with the family?		1. yes	2. no
If not:	1. left due to pregnancy	2. left due to HIV diagnosis	3. died
4. other	5. specify:		

Father

Age (years):	Primary caregiver: 1. yes		2. no
HIV status	1. unknown	2. positive	3. negative

Relationship status	1. single	2. partner	3. married	Duration (2/3):
Are you married to the child's mother?		1. yes		2. no

If caregiver is not the mother, has:	1. she died	2. abandoned child	3.other, specify:

Education (level attained):

Are you employed?	1. yes	2. no	Nature of work:

Does the child's mother help with money?	1. yes	2. no

Does anyone else help financially?		1. yes	2. no
Who?	1. your parent	2. other family	3. another partner
4. your sibling	5. friend	6. other, specify:	

APPENDIX 5: INITIAL ASSESSMENT - PAGE 2

Do you receive a grant?	1. yes	2. no
Child support grant	Care dependency grant	Disability grant (self)

Is other parent living with the family?		1. yes	2. no
If not:	1. died	2. left due to HIV diagnosis	
4. other	5. specify:		

Primary caregiver who is not a parent

Age (years):	Primary caregiver: 1. Yes 2. no

Relation to child?	1. Maternal grandmother
2. Paternal grandmother	3. Aunt
4. Other	Specify:

HIV status	1. unknown	2. positive	3. negative

Relationship status	1. single	2. partner	3. married	Duration (2/3):

If caregiver is not the mother, has:	1. she died	2. abandoned child	3.other, specify:

Education (level attained):

Are you employed?	1. yes	2. no	Nature of work:

Does the child's mother help with money?	1. yes	2. no

Does anyone else help financially?		1. yes	2. no
Who?	1. child's father	2. other family	3. your partner
4. your sibling	5. friend	6. other, specify:	

Do you receive a grant?	1. yes	2. no
Child support grant	Care dependency grant	
Foster child grant	Disability grant (self)	

Housing information

Suburb of residence:

Type of dwelling:	1. formal	2. informal	3. other
Serviced (water):		1. yes	2. no
Serviced (electricity):		1. yes	2. no

Access to a functioning refrigerator:	1. yes	2. no

Who owns the home:

Support system (HIV- infected parent)

Does someone help you when you are ill:	1. yes	2. no

Who:	1. other parent	2. another partner	3. your parent
4. your sibling	5. other family	6. other (specify):	

APPENDIX 5: INITIAL ASSESSMENT - PAGE 3

Disclosure information (HIV-infected parent)

Is child's other parent aware of your HIV status:	1. yes	2. no

Is child's other parent aware of child's HIV status:	1. yes	2. no

Is other parent's HIV status known:	1. yes	2. no

Is your mother alive:	1. yes	2. no
Does she know your and your child's status:	1. yes	2. no
Is she supportive:	1. yes	2. no

Where does she live (suburb):

II. ASSESSMENT OF CHILD

Date of Birth: _____/_____/_____ (dd/mm/yyyy) Sex: M F

Age at registration (months): _____

Perinatal / early infancy history

Gestational age at birth	weeks
Birth weight	grams

MTCT intervention	1. yes	2. no	
Details of programme:			
Early infant feeding	Breast only	Formula only	Mixed

Immunization during the first 2 years of life

BCG	Polio drops	DPT	Hib	Hepatitis B	Measles

Developmental milestones (Appendix 8)

PARAMETER	FUNCTIONING AGE IN MONTHS
Gross motor	
Fine motor	
Hearing / speech	
Personal / social	
DQ*	

*Developmental quotient (DQ) = [functioning age / chronological age] X 100

APPENDIX 5: INITIAL ASSESSMENT - PAGE 4

Previous hospital admissions in the last 2 years

Date	Where	Duration (days)	Diagnosis

Previous tuberculosis

Previously treated for tuberculosis?	1. yes	2. no

Date	Where	Duration (months)	Strength of diagnosis•

• World Health organisation classification: 1 = definite, 2 = probable, 3 = definite (Appendix 11).[29]

Clinical features

Growth and nutrition (current)

Body mass (kg):	**Percentile:**	**Z score:**
Length (cm):	**Percentile:**	**Z score:**
BMI (W/H^2):	**Percentile:**	**Z score:**
W/H z score:	Head circum (cm):	**Percentile:**
MUAC (cm):	**Percentile:**	**Z score:**
Peripheral oedema?	1. yes	2. no

Recent body mass recorded in the clinic recorded at least 30 days prior to the current date

Date when mass recorded:		Age (months):
Body mass (kg):	**Percentile:**	**Z score:**

APPENDIX 5: INITIAL ASSESSMENT - PAGE 5

Clinical features and complications of HIV infection (current)

Generalised lymphadenopathy	1. yes	2. no
Hepatomegaly	1. yes	2. no
Splenomegaly	1. yes	2. no
Dermatitis Active papular urticaria	1. yes	2. no
Active eczema	1. yes	2. no
Active impetigo	1. yes	2. no
Active molluscum contagiosum	1. yes	2. no
Active other	1. yes	2. no
Inactive / evidence of old lesions	1. yes	2. no
Digital clubbing	1. yes	2. no
Parotitis	1. yes	2. no
Oral candidiasis (≥ 2 months)	1. yes	2. no
Chronic otitis media (≥ 30 days)	1. yes	2. no
Chronic diarrhoea (≥ 30 days)	1. yes	2. no
Chronic lung disease♣ (unspecified)	1. yes	2. no
Lymphoid interstitial pneumonitis	1. yes	2. no
HIV encephalopathy (criteria) 1. DQ < 75% or regression	1. yes	2. no
2. Microcephaly	1. yes	2. no
3. Motor deficit	1. yes	2. no
HIV encephalopathy present (at least 2 criteria)	1. yes	2. no
Cardiomyopathy	1. yes	2. no
Nephropathy	1. yes	2. no
Other (specify):		

♣ Clinical and / or radiological features persisting for ≥ 6 weeks

CDC clinical classification (Appendix 1):

Laboratory findings

Mantoux:	
Viral load (copies / mL)	
Log_{10} viral load	
CD4+ count (x 10^9/L)	
CD4+ count (percentage)	

CDC immunological classification (Appendix 1):

Haematology results		Interpretation (↑, N, ↓)	Grading if Abn. (Appendix 6)
Hb (g/dL)			
MCV (fL)			
WCC (x 10^9/L)			
Neutrophils (x 10^9/L)			
PLT count (x 10^9/L)			

APPENDIX 5: INITIAL ASSESSMENT - PAGE 6

Chemistry results		Interpretation (↑, N, ↓)	Grading if Abn. (Appendix 6)
Bilirubin (μmol/L)			
Conjugated bilirubin (μmol/L)			
Aspartate transferase (U/L)			
γ-glutamyl transferase (U/L)			
Pancreatic amylase (U/L)			
Cholesterol (mmol/L)			

III INITIAL THERAPY

Antiretroviral therapy

Drug	Dosing instruction

Other medication

Drug	Dosing instruction

APPENDIX 7: FOLLOW-UP ASSESSMENT DATASHEET – PAGE 1

Name
DOB
Folder number
Registration number

Drugs
1._____
2._____
3._____
4._____
5._____
6._____

Status at start of ARV treatment
Clinical cat:
Immune cat

Visit	Date	Mass	Length	HC	MUAC	Comments

SERIOUS OR SEVERE ADVERSE EVENTS / SERIOUS ILLNESSES

1.
2.
3.
4.

APPENDIX 7: FOLLOW-UP ADHERENCE DATASHEET - PAGE 2

Registration number:_____ Start of ARV (date): _____

Medicine	Dose	Times / day	Date commenced	Date stopped / changed
1.				
2.				
3.				
4.				
5.				

Medicine	Adherence	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
Medicine	**Adherence**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32**	**Wk 36**
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs: Expected usage: Actual usage: % Adherence:					
Medicine	**Adherence**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					
	Dispensed (ml or tabs): Expected usage: Actual usage: % Adherence:					

APPENDIX 7: FOLLOW-UP ILLNESS AND ADVERSE EVENTS DATASHEET - PAGE 3

Registration number:_____Start of ARV (date): _____

Symptom, sign, illness[1] or adverse event	Onset date	Resolution date (leave blank if continuing)	Intensity 1=mild / grade 1 2=moderate / grade 2 3=severe / grade 3 4=very severe / grade 4	Relationship to ARV 1=certain, 2=probable, 3=possible, 4=not likely, 5 = unrelated	Action taken regarding ARV 1=none, 2=dose reduced 3=interrupted, 4=discontinued, 5=dose increased	Treatment required (yes / no)

[1]Minor illnesses include: upper respiratory infection, oral thrush, otitis media, impetigo, diarrhoea requiring ambulatory treatment
Major illnesses include: TB, pneumonia (radiologically proven), pneumonia (clinical diagnosis), bacteremia/septicaemia, urinary infection, diarrhoea requiring hospitalisation, meningitis

APPENDIX 7: RESULTS SHEET - PAGE 4

Registration number:_____ Start of ARV (date): _____

Visit	Viral load (copies / mL)	Log_{10} viral load	CD4+ count (x 10^9/L)	CD4+ percent	Hb (g/dL)	MCV (fL)	Neutro-phils (x 10^9/L)	PLT (x 10^9/L)	Total bilirubin (μmol/L)	Conj. Bilirubin (μmol/L)	AST (U/L)	γGT (U/L)	Amylase (U/L)	Choles-terol (mmol/L)	Blood sugar (mmol/L)

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN[30] – PAGE 1

Note to the interviewer
WORDS IN ITALIC ARE INSTRUCTIONS TO THE INTERVIEWER
WORDS IN NORMAL FONT ARE TO BE READ IN INTERVIEW

This script is to be used with the Adherence Data Collection sheet. When placed side by side, questions correspond to answer blocks in the data collection sheet.
Circle appropriate answer of fill in tables according to the numbering key provided.

The interviewee should be the person actually primarily responsible for giving the medication. In order to establish who this is in a non-judgemental way it is necessary to read the introductory remarks to the interviewee BEFORE asking about who actually gives the medication, (PART A, question 1). If the interviewee is not the one who actually gives the medication, except under exceptional circumstances, it is best to stop the interview at this point and make arrangements for the person primarily responsible for giving the medications to come in at the next visit.

Older children may take responsibility for their medication themselves. The wording of questions should then be changed appropriately (e.g. take medicines instead of give medicines, omit "CHILD'S NAME", etc).

Hallo. I am …….. We're trying to find out how people are managing with giving the antiretroviral medicines to their children. So, I'd like to ask you some questions about how you are giving the medicines to (*CHILD'S NAME)* at home..

We know that there are many different medicines that you need to give at different times during the day. This can be difficult to do for many reasons. Some people find it hard to remember to give medicines, some may not be at home at the right time and forget to carry their medicines with them, some are confused about the instructions for so many medicines, some children refuse to take the medicines or spit them out, and sometimes people just feel like having a break from the hard work of sticking to the medicines.

It's important for us to know what you are actually doing at home, so that we can find ways to make the medicines easier to give and help all our patients to be able to use them. So don't worry about telling us that you are not giving the medicines. We want to know what is really happening, not what you think we want to hear. Your answers will not affect your access to antiretroviral medicines in any way.

All the information you provide is confidential. It will not be given to your relatives or friends, to anybody outside this clinic, to the government or to anyone else. You do not have to answer a particular question if you don't want to, and you are free to stop this interview at any time if you don't want to carry on. Do you have any questions before we start?

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 2

ADHERENCE QUESTIONNAIRE: STANDARDISED SCRIPT

PART A

The first thing we need to do is to find out who exactly gives the medicines at home:

1. Who is the person mainly responsible for giving the medicines to (*CHILD'S NAME*)?

(*For the interview to be worthwhile, this should be the interviewee. If not, except under exceptional circumstances, it is best to stop the questionnaire at this point and make arrangements for the person primarily responsible for giving the medications to come in at the next visit.)*

2. What is your relationship to (*CHILD'S NAME*)?

Now we need to make sure that we are both talking about the same medicines.

Medicines that directly fight HIV, the virus that causes AIDS, are called 'antiretrovirals'. There may be some other medicines as well as the antiretrovirals that you are giving (*CHILD'S NAME*) . All the medicines are important, but for now I am only asking you about the medicines that directly fight HIV, the antiretrovirals.

3. (a) Can you tell me what medicines you are supposed to be giving (*CHILD'S NAME*) to fight HIV?
(*Subjects can: name the drug, list its characteristics (the pink medicine) or identify special labelling features. Naming the drug correctly in ANY of these ways will score a '1' in the adherence table.)*

3. (b) For each drug mentioned: How many times a day are you supposed to give (*drug name or characteristics as mentioned above*)? Don't tell me how many spoons or how many pills you are supposed to give, just how many times a day?

If all drugs not mentioned, then you can prompt:
3. (c) Are there any other medicines to fight HIV that you are supposed to be giving

(*CHILD'S NAME*) ?
Repeat Q 3(b) above

Subject is specifically questioned about prescribed medicines not yet mentioned at this point:

3. (d) Are you supposed to be giving (*drug name and characteristics e.g.)* ?
Repeat Q 3 (b) above.

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 3

ADHERENCE QUESTIONNAIRE: STANDARDISED SCRIPT - CONTINUED

PART A – CONTINUED

5. Now for (*drug name and characteristics*) it looks to me like this medicine needs to be given ….. times each day.
(*State the correct number of doses, not the number mentioned in (4) above*).

5. (a) Think about yesterday. Did you give it all …. Times, or did you miss a dose? If so, how many doses did you miss?

5. (b) Think about the day before yesterday. That would have been ……. Did you give it all …. times, or did you miss a dose? If so, how many doses did you miss?

5. (c) Try to think back just one more day. That would have been…….. Did you give it all ……. times, or did you miss a dose? If so, how many doses did you miss?

Repeat Q 5 for each drug.

6. Some people find that they forget to give the HIV medicines on the weekend days. Did you miss out on giving any of the medicines last weekend?

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 4

ADHERENCE QUESTIONNAIRE: DATA COLLECTION SHEET

PART A

Child's Name: **Reg number:**	**Date of questionnaire:** **Weeks on ART: 12 24 48**

Question 1

Name the person answering questionnaire and primarily responsible for giving ARVs:

Question 2

1. child 2. biological mother 3. biological father 4. grandmother 5. other relative (specify) _____ 6. other (specify)_____

Questions 3 – 5: medication table

Special notes:
[1]First 3 columns to be filled in by pharmacist before interview
Expected doses = number of doses per 24 hour period, not number of pills/teaspoons

[2]Identification
1 – Medicine name or description volunteered without prompt
2 – Medicine name or description volunteered with prompt
3 – Acknowledged medicine when reminded
4 – Did not show any knowledge of medicine

[3]Doses missed
0 – if no doses missed
1 – missed one dose
2 – missed all doses

Complete before interview			***Complete during interview***				
Drug name[1]	Description[1] (Colour; special identifying labels)	Expected doses[1]	Identification by patient[2]	Reported prescribed doses	Doses missed[3]		
					Yester-day	2 days ago	3 days ago

Question 6

Yes No Don't know

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 5

ADHERENCE QUESTIONNAIRE: STANDARDISED SCRIPT

PART B

1. Since your last visit, have you used any special aids to help you remember to give the medicines or done anything to make it easier to give the medicine?

I am going to read you a list of some of the things that other people do. Please tell me if you have used any of these to help you to remember the medicines: (*read list*)
Have you done any of these things?
Have you done anything else to help you with giving the medicines?

2. Now I'd like to ask you about some of the things that make it difficult for you to give the medicines to (*CHILD'S NAME*).

Do you have problems with giving all of the medicines, some of the medicines, or do you have no problems with giving the medicines.
If none, proceed to question 5.
If some, proceed to question 4.
If all, proceed to question 3 and omit question 4.

3. (a) I am going to read you a list of the things that other people say make it difficult to give the medicines. Please tell me if any of these things make it difficult for you to give ALL the medicines. At this stage, don't mention problems that you only have with one or two of them. (Read list opposite page) Are there any other reasons why you find it difficult to give the medicines?

3. (b) For each problem identified: Is this a problem occasionally, about half the time, or almost always?

3. (c) (i) Do you experience more difficulty with some of the medicines than with others?
(ii) Can you say why you find it more difficult to give …… ?
Would you like me to read the list of reasons for not giving the medicines again?
(iii) For each problem identified: Is this a problem occasionally, about half the time, or almost always?
(iv) Are there any other medicines that you find particularly difficult to give?
(*If yes, repeat (iii) to (iv) until subject says none of the rest of the medicines are especially difficult to give*)

4 (a) Which medicines do you find difficult to give?
(b) I am going to read you a list of some of the things that other people say make it difficult to give some of the medicines.
Please tell me if any of these things make it difficult for you to *give (name/characteristics of 1st medicine identified as a problem*) or if there is another reason why it is difficult to give?
(c) Is this a problem occasionally, about half the time, or almost always?
(d) Are any of these things I've read out a problem with *(name/characteristics of 2nd medicine identified as a problem*)? Repeat (c). (*Continue in this way, repeating (d) and (c) until all medicines identified as problematic have been covered*)

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 6

ADHERENCE QUESTIONNAIRE: DATA COLLECTION SHEET

PART B

Question 1

Circle ALL methods used:

Special labels	Calendar/ diary	Alarms/bleepers	Activity of daily living triggers (e.g. brushing teeth) - specify:
Treatment partner	Disguise taste - specify:		Other - specify:

Question 2

All	some	none

Questions 3 & 4

Special notes on filling in table
[1]Write in name of medicine
For each problem: leave blank if not a problem; enter 1 – sometimes; 2 – often; 3 - almost always

Why difficult?	**All**	**Med 1**[1]	**Med 2**[1]	**Med 3**[1]	**Med 4**[1]
I was away from home					
I was busy with other things					
I just forgot					
There was too much medicine to give					
I was worried about the side effects					
I did not want others to notice me giving the medicine					
The medicine tastes bad					
My child refused to take the medicine or spat it out					
There was a change in daily routine					
I felt the medicine might be harmful to my child					
There are lots of people looking after the child and I am not always with him/her at the right time					
I was ill					
My child was ill					
I felt depressed					
I ran out of medicine					
My child was well					
Other, specify:					

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 7

ADHERENCE QUESTIONNAIRE: STANDARDISED SCRIPT

PART C

1) Do you attend a support group?
   a) Which one?
   b) When was the last time you went to a support group meeting?

2) Do you think the antiretroviral medicines are helping (*child's name*)?

3) Do you think the antiretroviral medicines make (*child's name*) sicker?

4) If you were to stop giving (child's name) the antiretroviral medicines, do you think he/she would get sicker?

Thank you for helping us by answering these questions.

APPENDIX 8: ADHERENCE QUESTIONNAIRE FOR CHILDREN – PAGE 8

ADHERENCE QUESTIONNAIRE: DATA COLLECTION SHEET

PART C

Question 1

Yes	No

(a)

Name of support group:

(b)

Less than 2 weeks ago	Within the last month	1-2 months ago	More than 2 months ago	Never

Question 2

Yes	No	Don't know

Question 3

Yes	No	Don't know

Question 4

Yes	No	Don't know

Questionnaire completed by:

_____

Interview conducted in: English Afrikaans Xhosa Other

Interpreter used Y / N

APPENDIX 12: ANNUAL EVALUATION - PAGE 1

Registration number (assigned to patient):_____

Date of completion: _____/_____/_____ (dd/mm/yyyy)

PRIMARY CAREGIVER

Relation to child	1. mother	2. father
3. other	Specify:	

HIV status	1. unknown	2. positive	3. negative
Has your health changed over last year?		1. improved	2. deteriorated

Are you employed?	1. yes	2. no	Nature of work:

Does anyone else help financially?			1. yes / 2. no
Who?	1. your parent	2. other family	3. partner
4. your sibling	5. friend	6. other, specify:	

Do you receive a grant?	1. yes	2. no
Child support grant	Care dependency grant	
Foster child grant	Disability grant (self)	

ASSESSMENT OF CHILD

Date of Birth: _____/_____/_____ (dd/mm/yyyy)

Age at registration (months): _____

Developmental milestones (Appendix 8)

PARAMETER	FUNCTIONING AGE IN MONTHS
Gross motor	
Fine motor	
Hearing / speech	
Personal / social	
DQ*	

*Developmental quotient (DQ) = [functioning age / chronological age] X 100

Previous hospital admissions in the last 2 years

Date	Where	Duration (days)	Diagnosis

APPENDIX 12: ANNUAL EVALUATION - PAGE 2

Previous tuberculosis

Previously treated for tuberculosis?	1. yes	2. no

Date	Where	Duration (months)	Strength of diagnosis•

• World Health organisation classification: 1 = definite, 2 = probable, 3 = definite (Appendix 11).[29]

Clinical features

Growth and nutrition (current)

Body mass (kg):	**Percentile:**	**Z score:**
Length (cm):	**Percentile:**	**Z score:**
BMI (W/H^2):	**Percentile:**	**Z score:**
W/H z score:	Head circum (cm):	**Percentile:**
MUAC (cm):	**Percentile:**	**Z score:**
Peripheral oedema?	1. yes	2. no

Clinical features and complications of HIV infection (current)

Generalised lymphadenopathy	1. yes	2. no
Hepatomegaly	1. yes	2. no
Splenomegaly	1. yes	2. no
Dermatitis Active papular urticaria	1. yes	2. no
Active eczema	1. yes	2. no
Active impetigo	1. yes	2. no
Active molluscum contagiosum	1. yes	2. no
Active other	1. yes	2. no
Inactive / evidence of old lesions	1. yes	2. no
Digital clubbing	1. yes	2. no
Parotitis	1. yes	2. no
Oral candidiasis (≥ 2 months)	1. yes	2. no
Chronic otitis media (≥ 30 days)	1. yes	2. no
Chronic diarrhoea (≥ 30 days)	1. yes	2. no
Chronic lung disease♣ (unspecified)	1. yes	2. no
Lymphoid interstitial pneumonitis	1. yes	2. no
HIV encephalopathy (criteria) 1. DQ < 75% or regression	1. yes	2. no
2. Microcephaly	1. yes	2. no
3. Motor deficit	1. yes	2. no
HIV encephalopathy present (at least 2 criteria)	1. yes	2. no
Cardiomyopathy	1. yes	2. no
Nephropathy	1. yes	2. no
Other (specify):		

♣ Clinical and / or radiological features persisting for ≥ 6 weeks

CDC clinical classification (Appendix 1):

APPENDIX 12: ANNUAL EVALUATION - PAGE 3

Laboratory findings

Viral load (copies / mL)	
Log_{10} viral load	
CD4+ count (x 10^9/L)	
CD4+ count (percentage)	

CDC immunological classification (Appendix 1):

Haematology results		Interpretation (↑, N, ↓)	Grading if Abn. (Appendix 6)
Hb (g/dL)			
MCV (fL)			
WCC (x 10^9/L)			
Neutrophils (x 10^9/L)			
PLT count (x 10^9/L)			

Chemistry results		Interpretation (↑, N, ↓)	Grading if Abn. (Appendix 6)
Bilirubin (μmol/L)			
Conjugated bilirubin (μmol/L)			
Aspartate transferase (U/L)			
γ-glutamyl transferase (U/L)			
Pancreatic amylase (U/L)			
Cholesterol (mmol/L)			

INITIAL THERAPY

Antiretroviral therapy

Drug	Dosing instruction

Other medication

Drug	Dosing instruction

ANNEXURE B: OFFICIAL LETTER OF ETHICAL APPROVAL FROM UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

UNIVERSITY OF CAPE TOWN

Research Ethics Committee
E52 Room 24,Old Main Building Groote Schuur Hospital, Observatory, 7925
Queries : Lamees Emjedi
Tel : (021) 406-6338 Fax: 406-6411
E-mail : lemjedi@curie.uct.ac.za

18 July 2003

REC REF: 261/2002

Dr B Eley
Paediatrics
Red Cross

Dear Dr Eley

ANTIRETROVIRAL THERAPY-GUIDELINES FOR THE TREATMENT OF A COHORT OF HIV-INFECTED CHILDREN AND THEIR INFECTED PARENTS AT RED CROSS CHILDREN'S HOSPITAL

Thank you for your letter to the Research Ethics Committee dated 13 July 2003.

*It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study on the 16 July 2003.*

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROF T. ZABOW
CHAIRPERSON

ANNEXURE C: BMC PEDIATRICS INSTRUCTIONS FOR AUTHORS

Instructions for *BMC Pediatrics* authors

General information

You are advised also to read About this journal, which includes other relevant information.

Submission process

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

To facilitate rapid publication and to minimize administrative costs, *BMC Pediatrics* accepts only online submission. The submission process is compatible with version 3.0 or later of Internet Explorer and Netscape Navigator, and with most other modern web browsers. It can be used from PC, Mac, or Unix platforms.

Files can be submitted as a batch, or one by one. The submission process can be interrupted at any time - when users return to the site, they can carry on where they left off.

See below for examples of acceptable word processor and graphics file formats. Additional files of any type, such as movies, animations, or original data files, can also be submitted as part of the publication.

During submission you will be asked to provide a cover letter. Please use this to explain why your manuscript should be published in the journal and to elaborate on any issues relating to our editorial policies detailed in the instructions for authors.

Assistance with the process of manuscript preparation and submission is available from the customer support team (info@biomedcentral.com).

We also provide a collection of links to useful tools and resources for scientific authors, on our Tools for Authors page.

Publication and peer review processes

Submitted manuscripts will be sent to peer reviewers, unless they are either out of scope or below threshold for the journal, or the presentation or written English is of an unacceptably low standard. They will generally be reviewed by two experts with the aim of reaching a first decision as soon as possible. Statistical reviewers are also used where required (for a full list of our statistical advisers, please click here). Reviewers are asked to declare any competing interests and have to agree to open peer review, which works on two levels: the authors receive the signed report and, if the manuscript is published, the same report is available to the readers. The pre-publication history (initial submission, reviews and revisions - see, for example, pre-publication history) is posted on the web with the published article.

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In press article

3. Kharitonov SA, Barnes PJ: **Clinical aspects of exhaled nitric oxide.** *Eur Respir J*, in press.

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ANNEXURE D: CHOICE OF MEDICATION RETURN (MR) ADHERENCE MEASURE

The protocol stated that MR adherence data would be examined to determine the best composite measure of adherence for all three drugs over the year. The guiding principles for selecting the best composite MR adherence measure were (i) ability to predict viral suppression and (ii) clinical relevance, simplicity and explicability. The following approaches to calculating such a composite measure were explored:

(i) Mean monthly adherence: For each month for which medications were returned, the sum of the percentage adherence for all drugs was divided by the number of ART drugs prescribed (3) to determine mean adherence for that month. Association of mean monthly adherence and viral suupression was examined using an adjusted robust longitudinal logistic regression model clustered on patient.

(ii) Minimum monthly adherence for any drug: The association between the lowest percentage adherence for any drug during each month for which medications were returned and viral suppression was examined using an adjusted robust longitudinal logistic regression model clustered on patient.

(iii) Mean annual adherence: The sum of all mean monthly adherence measures (as calculated in (i) above) was divided by the total number of months for which medications were returned to obtain a mean annual adherence. Association with viral suppression was examined using logistic regression.

Results of univariate associations of each of the potential adherence measures with viral suppression are shown below. For each measure of adherence , cut-offs of ≥90% or ≥95% for "good adherence" were examined, however results using the threshold of ≥95% are shown for mean annual adherence only by way of example, as this threshold performed worse in terms of predicting viral suppression for all potential measures of adherence.

Table 7: Univariate associations between different composite measures of MR adherence and viral load <400 copies/ml after 1 year on ART

Adherence measure	Unadjusted OR	95%CI
Mean annual MR adherence ≥ 90%	10.30	1.92 – 55.67
Mean annual MR adherence ≥ 95%	2.56	0.97 – 6.72
Mean monthly MR adherence ≥ 90% (clustered on patient)	2.24	1.33 – 3.76
Minimum monthly adherence ≥ 90% (clustered on patient)	1.54	0.84 – 2.84

Mean annual MR adherence ≥90% was selected as the best composite measure of adherence. Not only did this measure demonstrate the greatest magnitude of effect in terms of viral suppression, it is also the simplest and easiest to explain and understand clinically.