COMPARISON OF SELF-REPORT AND PHARMACY PILL COUNT AS MEASURES OF ADHERENCE TO ANTIRETROVIRAL THERAPY IN CHILDREN AT KENYATTA NATIONAL HOSPITAL

A DISSERTATION PRESENTED IN PART FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PAEDIATRICS AND CHILD HEALTH AT THE UNIVERSITY OF NAIROBI

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DECLARATION

I certify that this dissertation is my own original work and has not been published elsewhere nor presented for a degree in any other university.

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DEDICATION

This work is dedicated to the best children in the world; Cherop and Noël, and to my loving husband Tom Ng'eno.

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LIST OF ABBREVIATIONS

RNA.....	Ribonucleic Acid
VL.....	Viral Load
AIDS.	Acquired Immune Deficiency Syndrome
ART.....	Antiretroviral Therapy
UNAIDS.....	United Nations Programme on HIV/AIDS
WHO.....	World Health Organization
KNH.....	Kenyatta National Hospital
CD4.....	Cluster Of Differentiation Subset 4
HAART.....	Highly Active Antiretroviral Therapy
HAZ-scores.....	Height for Age Z scores
WAZ scores.....	Weight for Age Z scores
WHZ-scores	Weight for Height Z scores
MEMS.....	Medication Event Monitoring Systems
CCC.....	Comprehensive Care Clinic
SPSS.....	Statistical Package for the Social Sciences
MSH –ART tool.....	Medical Sciences for Health antiretroviral Therapy tool
PENTA.	Paediatric European Network for Treatment of AIDS
PACTG.....	Paediatric Aids Clinical Trial groups
SD.....	Standard Deviation
IQR	Inter-quartile Range
OR	Odds Ratio

ABSTRACT

Background

Assessment of adherence is an essential component of monitoring antiretroviral therapy. In Kenyatta National Hospital, self/caregiver reported adherence is used to assess adherence. It is not known how this subjective method of measuring adherence compares with the more objective pharmacy pill count method.

Objective

The objective of this study was to compare caregiver reported adherence and pharmacy pill count adherence and to correlate both methods with the patients' clinical and immunological outcome and to describe the characteristics (sociodemographic, economic and clinical) associated with adherence.

Study Methods:

This was a cross sectional study whereby caretakers of children who presented to the routine paediatric HIV clinic from November 2007 to February 2008 were subjected to a structured interview to establish self-reported adherence for the two weeks prior to the clinic day. The patients' pharmacy pill count records for the prior month were abstracted from the MSH-ART dispensing tool and these were used to compute adherence rates. CD4 counts, percentages and anthropometric measurements were abstracted from the patients' clinical records. Adherence rates by the two methods were compared and then correlated with the patients' response to treatment.

Results

Mean adherence rate by pharmacy pill count for 1 month was 61% and 87% by caregiver reported adherence by use of 2-week recall. There was a significant difference when the two adherence rates by the two methods were compared (p <0.001). We did not find a difference in the clinical and immunologic response when patients were classified as adherent and non-adherent by either pharmacy pill count or self report. The caregiver and child's sociodemographic characteristics did not influence adherence. However we did draw firm conclusions on our findings on associations of adherence and patient response and on the correlates of adherence because this study did not have adequate power to answer these questions.

Conclusions

Caregiver report gave higher adherence rates compared to pharmacy pill count. There was no difference in clinical and immunological parameters between patients who were adherent and those who were not adherent.

Recommendation

There is need to incorporate pharmacy pill count as a method of assessing adherence during the routine clinical care of HIV-infected children at the KNH paediatric CCC.

INTRODUCTION AND LITERATURE REVIEW

The Global Impact of HIV on children

Of the 40.3 million people living with HIV, Children below 15 years constitute 2.3 million. Children constitute 700,000 of the 4.9 million of new global HIV/AIDS infections and 570,000 of 3.1 million of HIV/AIDS deaths annually. The burden of paediatric HIV-1 infection globally is highest in sub-Saharan Africa, with over 2 million children infected currently. By the end of 2006 there were 14 million orphans due to HIV-AIDS.[1] It has been estimated that at a global level, 660,000 children require antiretroviral therapy, the majority (91%) of whom reside in sub-Saharan Africa However, presently, less than 10% of all antiretroviral treatment occurs in children.[2]

Kenya is home to an estimated 150,000 children who are infected with HIV/AIDS with an estimated 34 000 new paediatric infections in 2004 alone. Statistics suggest that 30,000 to 40,000 of these children require ART. Yet only 7,800 children were on treatment by the end of 2006.[1]

Globally there have been tremendous efforts to provide HIV treatment to all children that need it. In 2005, United Nations Joint Programme on HIV/AIDS (UNAIDS) and United Nations Children's Fund (UNICEF) issued a global call to action that challenges the world to ensure that antiretroviral therapy or antibiotic prophylaxis, or both, reaches 80% of children in need by 2010.[2]

Also levels of funding for treatment have increased greatly due to initiatives like the United States Presidential Emergency Plan for AIDS Relief (PEPFAR) and Global Fund to fight HIV, AIDS and Malaria. Likewise in response to the AIDS pandemic, WHO has outlined a public health approach to therapy, simplifying and standardizing treatment regimen. A key to this approach is national consensus on one or more WHO-recommended first-line treatment regimens, along with second-line therapy for those whose first-line treatment fails.[3]

All HIV-1 infected Kenyan children are initiated on a standard first line regimen as recommended by the World Health Organization (WHO) and the Kenyan national guidelines.[3,4] Presently, comprehensive care including provision of ART, Cotrimoxazole prophylaxis, and supportive care for HIV infected children is available at KNH paediatric HIV clinic.

It is widely recognized that adherence to ART is a primary predictor of viral suppression, progression to AIDS and death.[5,6,7] As a result, clinical guidelines recommend regular measurement of adherence and in most clinics, self-report is the most feasible method.[8] Although assessments of adherence to highly active antiretroviral therapy in Africa are emerging, the validity of the adherence measurement strategies developed in resource-rich settings for use in resource-limited settings has not been fully investigated.[9,10,11]

Efficacy of Antiretroviral Therapy in children

The benefits of ART in the management of HIV disease in children are well established. Studies have shown that large and sustained CD4 cell count gains are possible regardless of baseline CD4 cell count so long as patients are adherent to ART.[12, 13,14,16]

This leads to a reduction in morbidity, mortality and improves the well being of the patients. In a recent study by Wamalwa et al, Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI) based first-line antiretroviral treatment was shown to be highly efficacious in HIV-1 infected Kenyan children.[13]

Comparable results were obtained in Thailand. In this study, Puthanakit et al, showed a remarkable virologic response in a prospective cohort of treatment-naive children with advanced stage HIV infection.[15]

Factors that may result in poor Antiretroviral response despite good adherence

Adherence is not the only determinant of ART failure or success. Other factors include genetic differences in drug metabolism, level of immune suppression at baseline, prior drug resistance, concurrent opportunistic infections and low potency of the antiviral regimen.[17]

Most of the children are diagnosed at late stages of HIV disease and with a more advanced immunologic decline. This may predispose to failure of antiretroviral therapy in these children because the host immune response plays a major role in controlling HIV-1 disease.[16,18] A high initial viral load, common in infants and young children, may also favor the selection of resistant strains because of a larger genetic repertoire and this may result in poor response to treatment.[19]

Importance of adherence to ART

Adherence to ART is one of the potentially modifiable factors that determine outcomes for patients with HIV. The consequences of poor adherence include sub-therapeutic drug blood concentrations. This leads to poor virological control, a higher viral load and selection of viral strains that are resistant to ART and therefore progression of HIV disease.[5] Additionally, the transmission of drug-resistant HIV has been well documented.[20] Therefore, accurately measuring adherence to ART plays a central role in efforts to improve it and therefore this provides the ability to sustain benefits of ART to the patient.

HIV treatment is demanding because one is required to take drugs at the same time every day. Studies have shown that >95% adherence is necessary to achieve therapeutic success (a non detectable virus load, a greater increase in CD4 lymphocyte count, and reduced rate of hospitalization) in at least 80% of treated patients.[7,21] Practically this means missing fewer than 3 doses over an entire month in a twice daily dosing regimen.

The need for high levels of adherence has been demonstrated. Studies have shown that small differences in levels of adherence are associated with substantial differences in virologic outcome.[7, 21] For example a study by Paterson et al to determine adherence rates to antiretroviral therapy and outcomes in adults, in the HIV clinics, 78% virologic suppression occurred at 95% adherence or more as compared to 45% virologic suppression at 90%–95% adherence. In this study, adherence rates were measured by using a microelectronic monitoring system.[7]

However, despite what has been observed about high levels of adherence, studies indicate that children on antiretroviral therapy find it difficult to be perfectly adherent.[15, 19]

Rates of adherence to Antiretroviral Therapy in children

Studies on adherence to ART in populations of children with HIV infection have reported sub-optimal adherence rates ranging from 58 to 89% depending on definitions of adherence, modes of assessment and duration of treatment assessed.[10,19,22,34] Self-report has generally been shown to overestimate adherence. Lower adherence rates are obtained when more objective measures like pharmacy pill count and MEMs are used.[19,22] Farley et al in a study on children compared MEMS, pharmacy pill counts and self-report methods and found adherence rates of 81.4%, 92 %, and 100 % respectively.[22]

Factors that may lead to poor drug adherence

Generally there is limited availability of paediatric formulations of antiretroviral drugs and also some of these drugs are unpalatable. There are also fears of drug toxicities and their side effects.[23] The younger children depend on caregivers to take their medication.[21] Therefore antiretroviral treatment for children is often highly demanding because it involves introducing multiple, strictly timed doses of several drugs into the caregiver and child's daily life.[19,24] This leads to infringement on the child's normal activities, especially as the child ages. All these factors may result in repeated potentially unpleasant child-caregiver encounters. This is additive to the adult issues of accurately identifying varied pills and liquids, integrating multiple medications into daily activities, as well as maintaining privacy.[11]

In most cases, children living with HIV disease and their families are often confronted with stressors like poverty and limited resources for caregiver and child support and these can present significant barriers to maintaining full adherence.[21] Most of these children are orphaned or live with sick parents. Such family disruptions may lead to lack of consistency of the caregiver with the child being tossed form one caregiver to the next. Stigma and discrimination are primary concerns of caregivers who often choose not to disclose information about the child's HIV status to family members or others.[25] Also some caregivers decide not to tell their children that they have HIV disease until adolescence, potentially impeding their cooperation with treatment.[21] All these impair the families' ability to manage the child's illness, including the proper administration of medications.

Some cultural practices have been identified as barriers to adherence. Some patients may view HIV/AIDS as a curse, which can only be overcome by divine intervention. For example a study by Wanyama et al on adults in Kampala-Uganda showed that patients believe in spiritual healing led patients to be non-adherent.[26] The family's beliefs concerning the treatment of HIV is important because the family members are usually the decision makers regarding the child's treatment.

There have also been concerns regarding whether those achieving high levels of adherence are able to sustain them.[10]There is therefore need to assess adherence accurately and regularly and to adopt measures to promote continuous adherence.

TOOLS FOR MEASURING ADHERENCE

There is no gold standard method for measuring adherence. The most commonly used methods are self-report or care giver report, pill counts, prescription refill monitoring, and electronic monitoring devices such as Medication Events Monitoring Systems (MEMS). Surrogate markers, particularly viral loads and CD4 cell counts have been used to gauge the ability of these tools to measure adherence. Directly Observed therapy has been attempted but has been found not feasible.

Use of Self /Caregiver Report to measure adherence

To date, self-report is the most readily accessible tool for measuring adherence to antiretroviral therapy or any other drug therapy.[4] It is easy to obtain data in the course of routine clinic visits and during the interview the clinician may be able to understand the dynamics surrounding missed medication. Self-Report also emphasizes the active role of caregivers and patients in their own care.[5]

Consequently, it is expected that patient and caregivers report will remain an important tool for measuring adherence to HAART.

Several studies have shown that, reported adherence predicts the virologic response to HAART and is a useful measure of adherence.[5,28] In a retrospective cohort study on adults to determine long-term utility of measuring adherence by self-report in a routine clinic setting in Melbourne, Australia, self reported adherence correlated with viral loads.[27]

Self/caregiver reports are subjective and are prone to over reporting. Studies have shown that self-reported rates of antiretroviral adherence average 5% to 20% greater than rates derived from electronic monitoring, and pharmacy records, resulting in the consensus that self-reports tend to overestimate adherence.[6,27,28,29] For example Arnsten et al, in a 6-month observational study to compare electronically monitored (MEMS) with self-reported adherence in adult drug users, found that mean self-reported one-week adherence was 78%. Mean MEMS 1-week adherence was 53%. In this study MEMS adherence predicted viral suppression better when compared to self-report.[6]

Nonetheless, studies have shown that despite overestimating adherence, self-reported adherence is still significantly associated with viral suppression. Also a correlation has been observed between self-reported non-adherence and virologic failure.[6,30] Therefore although less sensitive than other measures used in research, self-reported adherence is clinically relevant. The main task of the clinician is to elicit the self-report in a manner that maximizes its likelihood of revealing non-adherence.

Self/care-giver reports have been used in the past to estimate adherence to ART in cross sectional studies on children. Several studies have shown that reported adherence assessed over short periods like one day or one week correlates well with virologic and CD4 response.

Van dyke et al in the PACTG estimated adherence in a study on children by use of three-day recall. This was done at the evaluable visit of study defined as the 48th week of follow-up for 128 children and 24 or 36 weeks for the remaining 16 children.

In this study, full adherence was defined as no missed doses over the 3 days prior to the evaluable visit. There was a remarkable difference in viral suppression between the adherent and non-adherent groups. Full adherence was reported by 92 % (22 out of the 24) of the children with > 2 $\log_{10}$ drops in viral load from baseline to the evaluable visit and by 64% (62 out of 96) of the children with < 2 $\log_{10}$ drop in viral load ($p=.01$).[21]

Reddington et al obtained similar results in the Paediatrics Spectrum of HIV Disease (PSD) project. In this study 90 caregivers were interviewed about the child's adherence to medication in the prior 1-week. Viral loads were taken within one month of interview. They found that children whose caregivers reported no missed doses in the previous one week (adherent) were more likely to have a viral load of < 400 copies/ ml i.e. 50 % compared to only 24% of the non adherent children ($p=0.04$).[31]

Studies on adults have shown that self-reported adherence estimated using 24-hour recall was similar to reported adherence estimates measured over time on the same study subjects and this correlated well with viral load suppression. For example Arnsten et al sought to estimate self-report adherence on adults prospectively over 6 months. Patients were interviewed once every month both for 1 day and 1-week adherence information. The reported adherence levels in the 6 study visits did not differ significantly ($p=0.1$).

In the same study, one-day and 1-week adherence estimates did not differ significantly either, 79% and 78% respectively ($p=0.14$). This suggests that assessment of adherence for the immediate period preceding the clinic visit does provide an efficient and reliable measure of adherence and this can give insight to adherence levels in the past.[6]

Use of Pill Counts to estimate adherence

Pill counts can be conducted in the clinic, at unannounced home visits or in the pharmacy when the patient returns to refill the prescription. When unannounced, pill counts may provide a more accurate assessment of adherence rates than self-report. Pill count adherence is usually calculated by counting the remaining doses of medication and assuming that the remaining pills in excess of what is expected represent missed doses.[31] This means that the patients need to remember to come with all the extra drugs during the clinic visit.

This method has been shown to provide tangible evidence on adherence in children. For example in a study to compare various methods of assessing adherence (Pharmacy Pill Count, Self Report and MEMS) Farley et al estimated pharmacy pill counts and MEMs adherence rates over the 6-month study period. Caregivers were also interviewed once about the child's missed doses in the prior day, within 3 months after enrolment into the study. These children had been on treatment for duration of 0- 23 months with a median of 6 months. The respective adherence rates obtained were then compared with viral loads measured at the end of the study period (6 months). In this study, Pharmacy pill Count and MEMS adherence rates correlated well with viral suppression but there was no correlation between Self/Caregiver Reported adherence and viral suppression.[22]

The potential advantages of pill counts are;

- Not requiring accurate recall
- Being less susceptible to deception
- Allowing retrospective assessment and
- Being obtainable from computerized records.

The potential disadvantage is the lack of information on adherence patterns during the intervals.

STUDY JUSTIFICATION

The use of ART for children infected with HIV means the use of complex drug regimens, which is challenging to the patient and clinicians in terms of adherence. Because poor adherence can lead to poor viral suppression, clinical failure and development of drug-resistance to HIV, there is need to identify patients who are non-adherent. However this can only be done if adherence is measured accurately.

Clinicians at the KNH paediatric HIV clinic mainly rely on care-giver/self report where by information on missed doses in the prior one week is obtained and is used to determine adherence. Clinicians do not access the pharmacy pill count records yet they are available. This study sought to determine how the two measures of adherence compare with each other and their association with the patients clinical outcome. The aim was to establish if there is need for clinicians to access pharmacy pill count records while routinely assessing adherence in these children or they could rely on self-report alone for decision-making as is the practice.

STUDY OBJECTIVES

Main objective

To determine and compare adherence levels as measured by caregiver/self report over a two week period and pharmacy pill count records over a month period in HIV-1 infected children at Kenyatta National Hospital.

Secondary objectives

1. To determine the association between adherence rates by both pharmacy pill count and self report and immunologic response in HIV infected children on ART at KNH.

2. To determine the association between adherence rates by both pharmacy pill count and self-report and clinical response in HIV infected children on ART at KNH

3. To determine correlates of adherence in HIV infected children at KNH. Correlates of interest are: child's age, sex, socio-economic status, severity of illness at initiation of ART, child's knowledge of their HIV status and HIV status of caregiver.

MATERIALS AND METHODS

Study design: Cross sectional study.

Study setting: The paediatric Comprehensive Care Clinic at the Kenyatta National Hospital which is a teaching hospital for the University of Nairobi and a National referral hospital for Kenya. This clinic had approximately a total of 550 HIV infected children on follow up, 430 of whom were on ART as at October 2007.

Study Period: This study was carried out from November 2007 to February 2008.

Study Population:

HIV-1 infected children who were on follow up at the Kenyatta National Hospital Comprehensive Care Clinic. The age of these children ranges from weeks to 15 years.

Inclusion criteria

- Children whose caregivers gave informed written consent.
- Children who had been followed up for a period between six and eighteen months.
- Children with available pharmacy and clinical records.

Exclusion criteria

- Children who did not have pharmacy and clinical records.
- Children on second line therapy
- Children who were not accompanied by primary caregiver

Sample size calculation

The sample size calculation formula is as shown.[33]This is based on proportions from a study by Farley et al in children, which obtained mean adherence rates of 100% by self-report and 92% by pharmacy pill counts.[22]

$$n = \frac{2 * [Z_{crit} * sqrt(2P(1-P)) + Zpwr * sqrt(p_1(1-p_1) + p_2(1-p_2))]^2}{D^2}$$

$$= \frac{2 * [1.96 * sqrt(1.92*0.08) + 0.842 * sqrt(0.92*0.08)]^2}{(0.08)^2}$$

n=186

Where n = minimum sample size required

Sqrt = Square Root.

p_1 & p_2 = adherence proportions from Farley et al where p_1 is 100% (self reported adherence and p_2 is 92% (pharmacy pill count adherence).[22]

$P = (p_1 + p_2)/2$

$D = |p_1 - p_2|$

Both Z_{crit} & Zpwr are cut off points along the x-axis of the standard normal probability distribution that represents the 95% confidence interval (1.96) and a statistical power of 80% (0.842), respectively.

Sampling method

Every consecutive patient presenting at the CCC who fulfilled the inclusion criteria was recruited.

DEFINITIONS

Primary caregiver: The person who is responsible for giving the child medications.

Food supplement For the purpose of this study, this was the enriched porridge which is available at the KNH paediatric CCC and is availed by the clinic nutrionist to all children that need it.

Poor adherence: - Adherence rates of < 95% by pharmacy pill counts over the 1 month period prior to clinic visit.

- Reported adherence of < 95% in the 2 weeks prior to clinic visit.

Caregiver Reported adherence

This was calculated as follows:

$$\frac{\text{No of doses reported as taken over 2 weeks}}{\text{No of doses required to be taken over 2 weeks}} \times 100$$

Pharmacy pill count adherence

This was calculated as follows:

$$\frac{\text{Number of doses dispensed Over one month period}}{\text{No. Of doses prescribed for the one month.}} \times 100$$

Additional analysis of adherence rates

Pharmacy pill count adherence over the 6-month period prior to clinic visit

$$\frac{\text{Number of doses dispensed Over 6 months}}{\text{No. Of doses prescribed for the 6 months.}} \times 100$$

Adherence by use of three-day recall

Good adherence is defined by no reported missed doses in the three days prior to clinic visit (100% adherence)

Staging of HIV/AIDS Disease

The severity of HIV disease was defined according to the classifications shown below:

(a) Immunological Classification

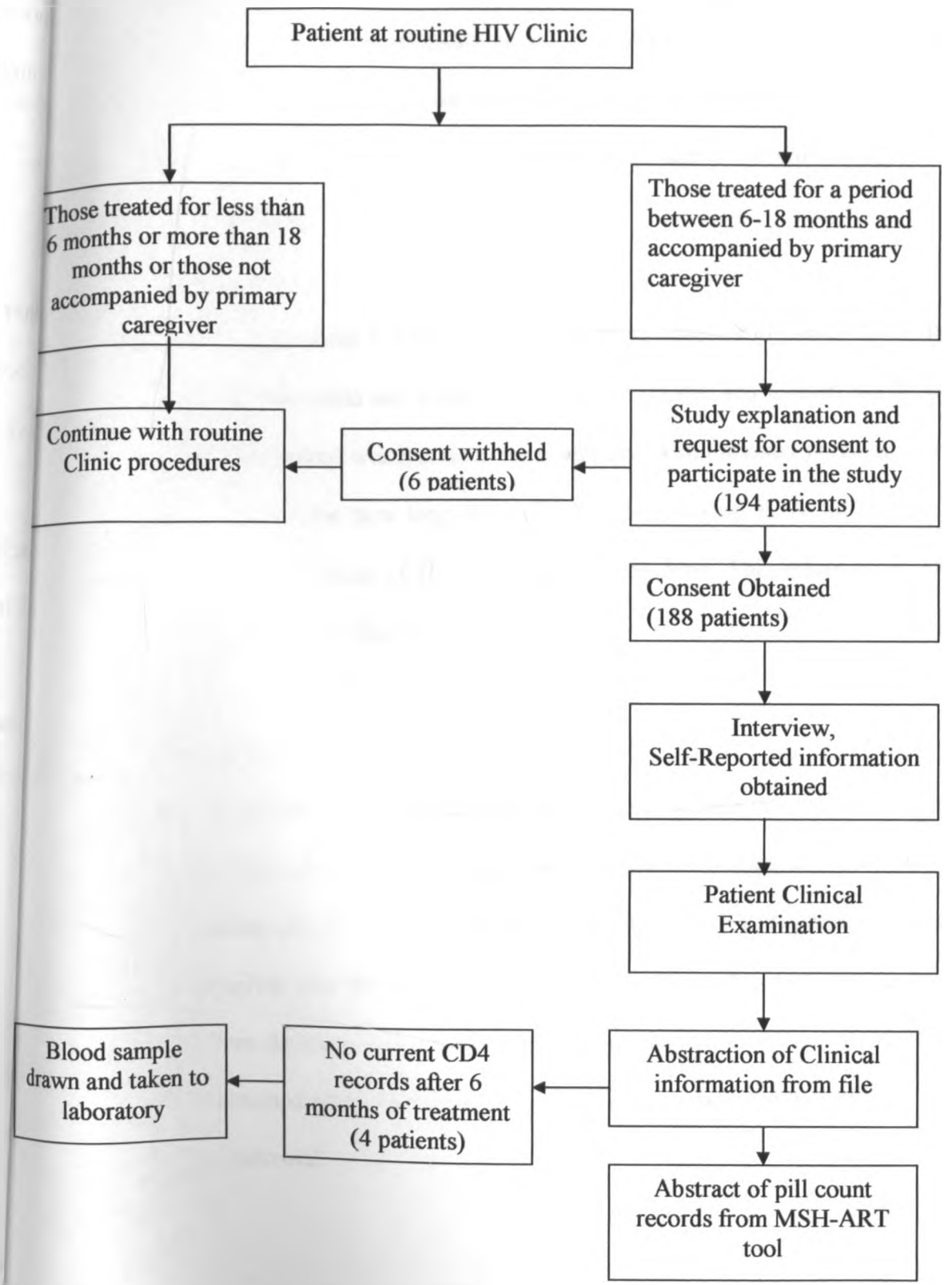
This was done according to WHO immunological staging (Revised in 2006).

Refer to appendix 5.

(b) Clinical Staging

This was done according to the WHO Paediatric clinical staging system (Revised in 2006). Refer to appendix 6.

METHODOLOGY FLOW CHART



STUDY PROCEDURES

The principal researcher and research assistants visited the study area from Monday to Friday between 8 to 5 pm during the study period. After explanation of the nature and purpose of the study, all caregivers whose children met the inclusion criteria were requested to give a signed informed consent (Appendix 1) and those consenting were then enrolled into the study.

The interviews were done using a standard questionnaire to obtain information from the caregivers to establish the child and caregiver sociodemographic and clinical variables. The caregiver was also asked whether they were supplied with enriched porridge from the CCC nutritionist and for how long the child had been taking it. A full physical examination and clinical staging of HIV of the child was done. This information was recorded in a proforma. (Appendix 2)

Self-Reported adherence

Caregiver reported adherence was assessed by use of a face-to-face structured interview with the caregiver. The interviewer first read a statement acknowledging that most people have difficulty taking all their HIV medication. The child's ARV regimen was then clarified. The caregiver was asked if the child had missed any doses of antiretroviral medicine in the three days and two weeks prior to the clinic visit. For the older children information was obtained from both caregiver and child and where the two differed, the child's report was followed.

If a child had missed any doses, further details were obtained as to the exact drugs involved, the number of doses missed and the reasons for missed doses.

Anthropometric measurements

Weight and height are measured at every clinic visit and are recorded in the patients file by a trained nurse. Weight is measured by use of a digital scale to the nearest 100 grams and length/height is measured by the use of a stadiometer to the nearest 0.5cm. Baseline and subsequent measurements of weight and height were obtained from the patients' records. These were recorded in a clinical data form. (Appendix 3)

CD4 counts and CD4 Percentage

For all the patients on treatment, CD4 counts and CD4% are done at baseline and 6 monthly thereafter. These are done in the University of Nairobi's paediatrics department laboratory at no charge to the patients. These are analyzed by an automated flow cytometry analyzer (FACScount, Becton Dickinson, USA). These are recorded in the patient's clinical file.

Absolute CD4 lymphocyte counts and CD4% percentages for the study period were obtained from the patient's clinical file. For those patients treated for more than 6 months and without a second reading of CD4 counts, two milliliters of blood were drawn and taken for analysis at the department of paediatrics (University of Nairobi). These CD4 counts were used to obtain the child's immunological stage of HIV.

Changes in CD4 counts and CD4 percentage over the study period was calculated as the difference between those done at baseline (at initiation of ART) and 6 months, 12 months and 18 months respectively. The baseline and subsequent CD4 counts and percentages were obtained from the patients' clinical records. A laboratory data abstraction form was used to record the patients CD4 counts and percentages. (Appendix 4) The baseline immunological staging was obtained from the patients' clinical records. The current immunological categorization was done as per the WHO (2006 Revision) immunological staging system. (Appendix 5)

Pharmacy pill count records

All patients who attend the clinic refill their prescriptions from the Comprehensive Care pharmacy on specified dates. This pharmacy uses a soft ware, MSH-ART dispensing tool to monitor adherence. (Appendix 7) This shows the patients demographic data, current regimen, dates when drugs were dispensed, drug formulation, quantities of doses dispensed, and the expected date for prescription refill. Drugs are dispensed for 30 days and patients are required to show the remaining medicine when they return for a refill and only the deficit is dispensed to total up to a 30 days supply. For the liquid formulations, liquid estimation is done by the use of a syringe. For those whose refill data was missing in the MSH soft ware, information was retrieved from the hard copy of the prescription on which the pharmacist also records information on returned doses. These hard copies are usually stored in the pharmacy. Prescription medication refill data was abstracted from the above pharmacy records and recorded in a pharmacy data abstraction form. (Appendix 8)

Ethical considerations

Written consent to carry out this study was obtained from the KNH ethical review Committee. Patients were enrolled into the study only after caregiver signed informed consent. They were explained to what the study entailed, the potential benefits and risks. The caretakers were also assured that they could withdraw from the study at any point and this would not affect the normal procedures in the clinic. The consent explanation was prepared in English and where need arose, it was verbally translated into a language that the caregiver and patient best understood.

The caregiver was assured of confidentiality and all interviews were conducted in a confidential manner and the information generated in this study was kept confidential. Caregivers were asked about the child's knowledge of his/her HIV status in the absence of the child. The study questionnaires were coded instead of bearing the patient's names. All study data was entered into a computerized database which was password protected and was only accessible to the study personnel.

The results of this study will be communicated to the clinical care staff and the CCC management at KNH for appropriate action.

Data analysis

All data was entered into SPSS version 14. The WHZ scores, HAZ scores and WAZ scores were computed using the nutrition software of Epi Info 3.2 (Centers for Disease Control and Prevention [CDC], Atlanta). This software sets a z score of 0 to correspond to the median score for the age and sex of a reference healthy population. Therefore for example, a score of -2 means 2 SD less than the median. Data was summarized into proportions percentages, means, medians, ranges, and standard deviations.

Adherence was analyzed both a dichotomous (adherent and non-adherent) and a continuous variable (expressed in percentage). Adherence rates by self-report and prescription refill records were compared by use of Mc Nemar test for paired tests. To investigate the association between adherence and clinical parameters, the t-test and Mann Whitney u were used as appropriate. The results are presented in the form of tables and bar charts.

STUDY RESULTS

Description of the study children

During the study period between November 2007 to February 2008, 194 caregivers bringing children to the routine paediatric comprehensive care clinic were approached for recruitment into the study. Six of them withheld consent and data was collected from 188 child-caregiver pairs and considered for analysis.

Table 1: Clinical characteristics of children at ART initiation

Characteristic (n=188)		Number	Percentage
Gender	Male	94	50
	Female	94	50
WAZ scores	≤ -3SD	24	13
	-3 to –2SD	41	22
	≥ -2SD	123	65
HAZ scores	≤ -3SD	29	15
	-3 to –2SD	32	17
	≥ -2SD	127	68
WHZ scores	≤ -3SD	24	13
	-3 to –2SD	41	22
	≥ -2SD	123	65
WHO clinical stage			
	I	14	7
	II	35	19
	III	109	58
	IV	30	16
		Median	Inter-quartile Range (IQR)
Age (years)		5	2,7
CD4 counts, cells/ul		379	157,732
CD4 Percentage		11	6,15

Out of the 188 children in the study, 94 (50%) were females giving a female to male ratio of 1:1. The children's median age was 5 years, IQR (2 to 7) years. The children's age ranged from 6 months to 12 years.

The children's clinical characteristics at the time of initiation of ART were abstracted from the clinical files. Majority of the children had no or mild malnutrition (≥ -3SD of WHZ scores, WAZ scores and HAZ scores) at initiation of therapy. The median absolute CD4 count was 379 cells/ul IQR (157,732) and that of CD4 % was 10.9 % IQR (6,15). Majority of the children started off with severe immunosuppression with 139 (74%) being in the WHO clinical stages III and IV. The rest 49 (26%) had WHO stages I and II disease.

Table 2: Socio-demographic characteristic of the children at time of interview

Characteristic (n = 188)	Frequency	Percentage
School attendance*		
Attending school	79	81
Not attending school	19	19
Parents Status		
Orphans	78	41
Full orphan	17	9
Mother dead	23	14
Father dead	38	22
Non orphans	110	59
Food Supplementation (enriched porridge)		
On supplements	43	23
Not on supplements	145	77
Duration of ART		
Up to 6 months	23	12
7 to 12 months	86	46
13 to 18 months	79	42

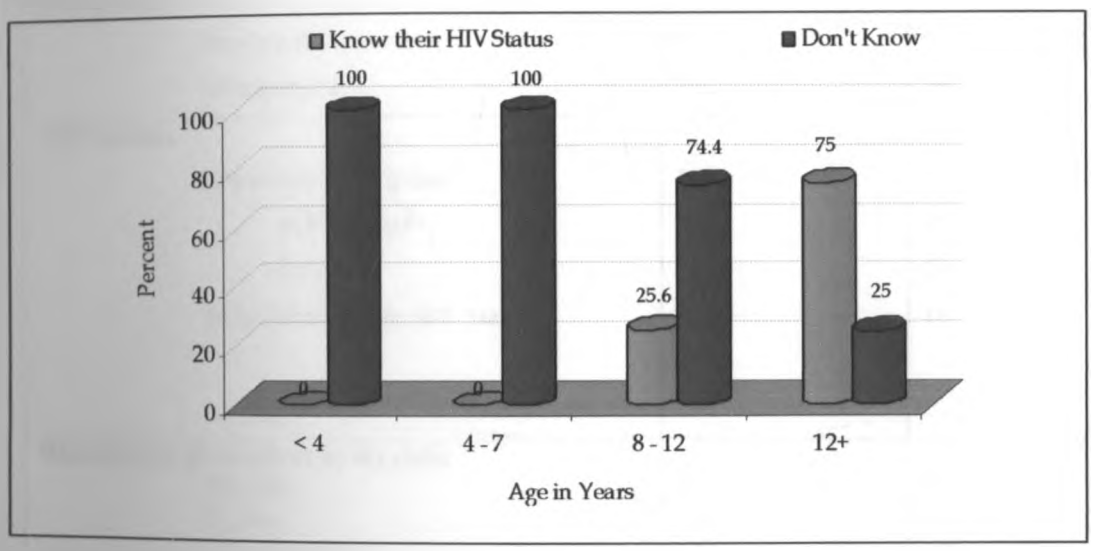
* Analysis confined to children who had attained the Kenyan primary school entry age (≥ 6years old).

Of the 98 (52%) children who were of school going age (≥ 6 yrs), 79 (81%) of them were attending school. Majority of the children, 110 (59%) were non-orphans while 78(41%) were orphaned.

Of the orphans, 17(9%) were fully orphaned, while the rest 61(32%) had one surviving parent only.

Forty-three of the children were receiving food supplements (enriched porridge). The shortest duration of treatment was 6 months and the longest was 18 months. The mean duration of treatment was 12 (± 0.3) months. Twenty three (12%) of the children had been treated for six months, eighty six (46%) and seventy nine (42%) for twelve and eighteen months respectively. This is illustrated in table 2 above.

Figure 1: Disclosure of HIV status to the child
(n=188)



At the time of study, a total of 19 (10%) of the children had been made aware of their own HIV status. Of these, none were below 4 years and there was also none between the age of 4 and 7 years. Of the children between 8 and 12 years (n=39), 10 (26%) knew their HIV status. Nine (75%) of the children between 12 and 15 years (n=12) were already aware of their HIV status. This is shown in figure 1 above.

Table 3: Caregiver sociodemographic characteristics at time of interview

Characteristic of caretaker (n =188)		Frequency	Percentage (%)
Gender	Male	33	18
	Female	155	82
Age distribution			
	≤20 yrs	3	2
	21-30 yrs	73	39
	31-50 yrs	101	54
	≥50 yrs	11	5
Level of Education			
	None	8	4
	Primary	54	29
	Secondary and tertiary	126	67
Occupation			
	Employed	117	62
	Unemployed	71	38
HIV status			
	Knew their HIV Status	158	84
	HIV infected	102	65 (102/158)
	On ARVs	55	54 (55/102)
	Did not know their HIV Status	30	16
Relationship of caregiver to the child			
	Mother	122	65
	Father	22	12
	Grandparents	12	6
	Other relatives (aunties, uncles cousins, siblings, step parents)	32	17

Out of the 188 caregivers in the study most were females with a female to male ratio of 4.7:1. Their median age was 32 years (range of 28 – 37 years). Majority of the caregivers (67%) had attained secondary education and beyond.

More than half of the caretakers were in some form of employment. One hundred and fifty eight (84%) of the caretakers knew their HIV status. More than half (65%) of those who knew their HIV status were HIV infected. Of the caregivers who were HIV infected, half (54%) were on ART. Only 30 (16%) did not know their HIV status.

One hundred and twenty two (65%) primary caregivers were mothers to the children, while 22 (12%) were fathers to the children. Thirty-four (18%) of the primary caregivers were not the children's biological parents.

This is shown in table 3 above.

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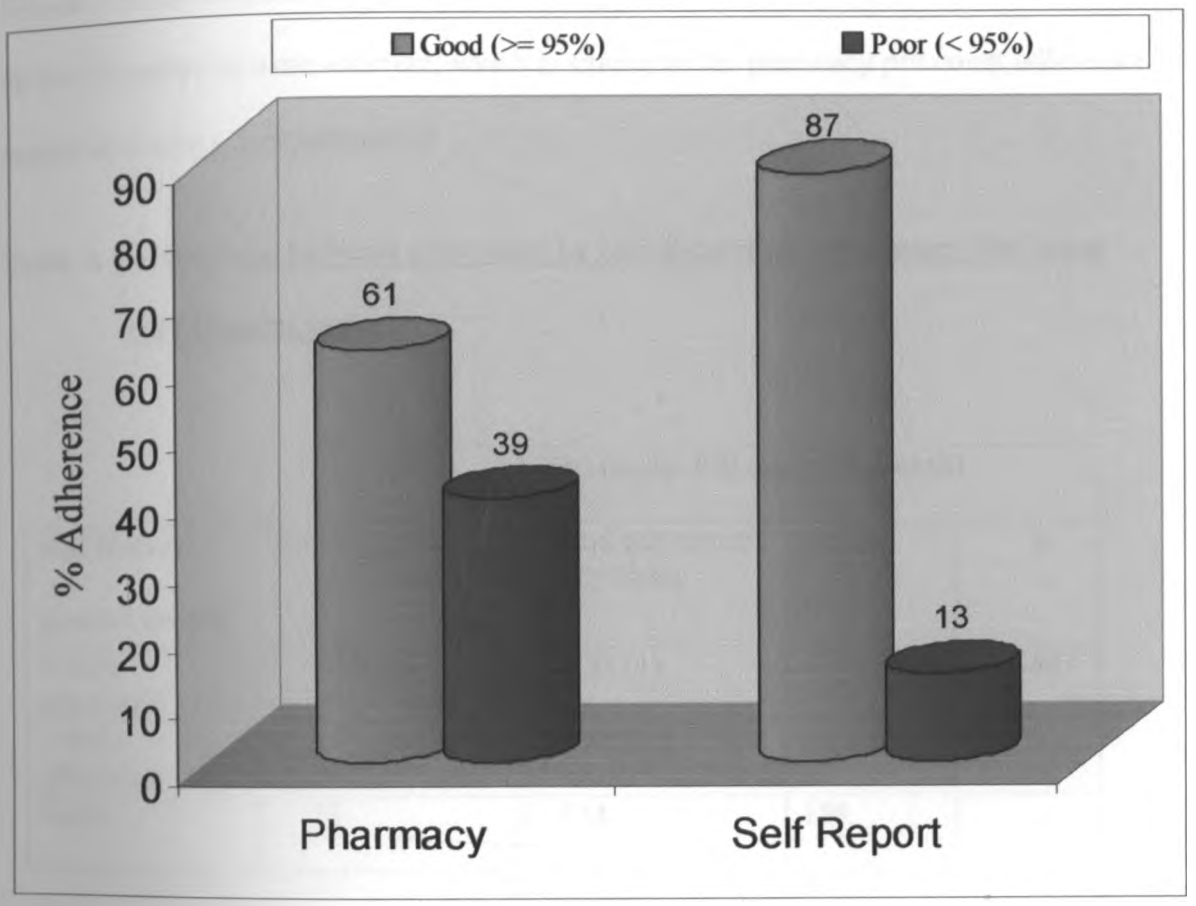
ADHERENCE LEVELS

Figure 2: Self-reported and pharmacy pill count adherence levels

(n = 188)



One hundred and fourteen patients (61%) had taken ≥95% of the dispensed doses in the 1-month period prior to the study while 74 (39%) had taken <95% of the dispensed doses. One hundred and sixty four (87%) of the children were reported to have taken all their doses in the two weeks days prior to the study while twenty-three (13%) had reported having missed some doses in the prior three days. This is shown in the figure 2 above.

Additional analysis of adherence rates

We used three-day recall to estimate reported adherence and found an adherence rate of 88% (165patients). These findings were similar to the 2 week reported adherence of 87%. Similarly when we estimated pharmacy adherence over a 6-month period we found that 58 % (109 patients) were adherent, which is similar to the pharmacy pill count adherence rate of 61% over a 6-month period.

Table 4: Comparison between adherence by Self-Report and Pharmacy Pill count (Mc Nemars test)

	Pharmacy Pill count (1 month)			
Self Report (2 week recall)	Poor adherence (< 95%)	Good adherence (≥ 95%)	Total	***p***
< 95% adherence	11 (15)	13 (11)	24	***<0.001***
≥ 95% adherence	63 (85)	101 (89)	164	
Total	74	114	188	

Table 4 above shows the comparison between caregiver-reported adherence for a period of 2 weeks and pharmacy pill count for a period of 1 month, using a cut off of ≥ 95% as good adherence by both measures. We found discordance between the two measures. Out of the 164 children who had good adherence by self-report, 63 of them were identified as non- adherent by pharmacy pill counts, while only 13 out of 114 children who had good adherence by pharmacy pill count were identified as non-adherent by self-report.

Pattern of reported missed doses and the reasons for the missed doses

Of the 24 (13%) patients who reported having missed doses, 4 did so once while 20 reported having missed more than one dose. Common reasons for missed doses included: change in daily routine 42% (10 of 24), drugs got finished before the next pharmacy appointment 25%(6 of 24), misunderstood the regimen 13%(3 of 24), child vomited without redosing 8%(2 of 24). One caregiver forgot to administer the medication to the child (4%), one reported that the drugs got lost while they were traveling upcountry (4%) and one withheld administering the medication because she had visitors and feared that some one could find out about the child's HIV status (4%).

Association between adherence and immunological response

In this analysis, patients were categorized into adherent and non-adherent by caregiver report using two-week recall. Similarly, patients were also categorized into adherent and non-adherent by pharmacy pill counts over the one-month period prior to the interview. We then compared the increments in CD4 counts between those patients who had good adherence and those who had poor adherence by the two adherence measures.

We analyzed CD4 counts and CD4 % at 6 and 12 months separately because their rate of increment has been shown to level off with time during treatment and therefore the expected rate of increment is different at different times. In this analysis, we excluded children treated for durations beyond twelve months because only 16 had analyzable data.

In the analysis of CD4 %, we used the mean because this data had a normal distribution. By the use of independent samples t-test we compared the mean increment in CD4% between those patients with good adherence and those with poor adherence.

To analyse the increment in absolute CD4 counts, we used the median because this data did not have a normal distribution. To compare the increment in CD4 counts between those patients with good adherence and those with poor adherence, we used the Mann-whitney U (non parametric) test.

Table 5: Association between Pharmacy Pill Count adherence and CD4 increment

Mean increase in CD4% (SD)*				
Duration of ART	n	Non adherent	Adherent	*P*
6months	177	7.4 (9.8)	9.3 (7.4)	*0.16*
12 months	77	11.3 (8.6)	10.8 (7.3)	*0.82*
Median increase in absolute CD4 Counts (IQR) **				
Duration of ART	n	Non adherent	Adherent	*P*
6 months	177	217(71,493)	279(121,610)	*0.14*
12 months	77	376(91,812)	432(231,657)	*0.59*

* Standard Deviation ** Interquartile Range

There was no significant difference in increments in CD4% between those patients with good adherence and those with poor adherence after 6 and 12 months of ART.

Similarly, there was no significant difference in the increment in absolute CD4 counts after 6 and 12 months of ART.

This is shown in table 5 above.

Table 6: Association between Self Reported adherence and CD4 increment

Mean increase in CD4% (SD)*				
Duration of ART	n	Non adherent	Adherent	*P*
6months	177	9.7 (9.0)	8.4 (8.4)	*0.48*
12 months	77	9.4 (7.1)	11.2 (7.8)	*0.52*
Median increase in absolute CD4 Counts (IQR)**				
Duration of ART	n	Non adherent	Adherent	*P*
6 months	177	140(52,366)	267(114,565)	*0.10*
12 months	77	178(75,611)	411(216,688)	*0.16*

* Standard Deviation ** Interquartile Range

There was no significant difference in the increment in CD4% between those patients with good adherence and those with poor adherence both after 6 and after 12 months of ART.

Similarly, there was no significant difference in the increment in absolute CD4 counts between those patients with good adherence and those with poor adherence both after 6 and 12 months of ART.

This is shown in table 6 above.

Association between adherence and clinical response

In this analysis, children were categorized into two groups. Those with good adherence and those with poor adherence by pharmacy pill count (for the one month period prior to the study). Patients were also categorized into adherent and non-adherent by Self-report (2 week recall).

Independent samples test was used to compare the increment in WAZ scores, HAZ scores and WHZ scores between children who had good adherence and those who had poor adherence.

We excluded children treated for durations beyond twelve months in this analysis because very few (49 children) had analyzable data.

Table 7: Association between Pharmacy Pill Count adherence and anthropometric Measurements

		Mean change in WAZ scores (SD) *		
Duration of ART	n	Non adherent	Adherent	*P*
6 months	180	-0.3(2.8)	0.42(2.0)	**0.028**
12 months	139	-0.2(1.5)	0.1(1.9)	*0.418*
		Mean change in HAZ scores (SD)		
Duration of ART	n	Non adherent	Adherent	*P*
6 months	180	0.6(1.2)	0.7(1.8)	*0.501*
12 months	147	0.5(1.3)	0.5(1.3)	*0.814*
		Mean change in WHZ scores (SD)		
Duration of ART	n	Non adherent	Adherent	*P*
6 months	180	0.7(1.6)	0.6(1.1)	*0.796*
12 months	139	0.9(1.8)	0.8(1.5)	*0.632*

SD* Standard deviation

Those children with good adherence by Pharmacy Pill count had a significantly greater increase in WAZ scores compared to those with poor adherence after 6 months of ART. However, there was no significant difference when we compared the increments in WAZ scores for those children with good adherence and those with poor adherence after 12 months of ART.

There was no significant difference when we compared HAZ scores between those patients with good adherence and those with poor adherence.

Similarly, we did not find any significant difference between the increment in WHZ scores between those patients with good adherence and those with poor adherence.
This is shown in table 7 above.

Table 8: Association between Self Reported adherence and anthropometric measurements

		Mean change in WAZ scores (SD) *		
Duration of ART	n	Non adherent	Adherent	*P*
6 months	180	0.2(1.3)	0.1(2.2)	*0.914*
12 months	139	-0.2(0.9)	-0.03(1.8)	*0.670*
		Mean change in HAZ scores (SD)		
Duration of ART	n	Non adherent	Adherent	*P*
6 months	180	0.7(1.4)	0.6(1.6)	*0.88*
12 months	147	0.2(9.4)	0.6(1.4)	*0.292*
		Mean change in WHZ scores (SD)		
Duration of ART	n	Poor adherence	Adherent	*P*
6 months	180	0.5(1.1)	0.7(1.4)	*0.607*
12 months	139	0.5(1.1)	0.9(1.7)	*0.315*

SD* Standard deviation

There was no significant difference in the increase in WAZ scores between those patients with good adherence and those with poor adherence after 6 and after 12 months of ART.

There was also no significant difference in the increment in HAZ scores between these two groups of patients.

Similarly, there was no significant difference between the increments in WHZ scores between those patients with good adherence and those with poor adherence.

This is shown in table 8 above.

CORRELATES OF ADHERENCE

UNIVARIATE ANALYSIS

Table 9: Correlation of caregiver characteristics to adherence by pharmacy pill counts

Characteristics	Good Adherence Frequency (%) n=114	Poor Adherence Frequency (%) n=74	Odds Ratio (95% CI)	P
Caregiver knows HIV status	99 (87)	59 (80)	1.7(0.7-3.7)	*0.193*
Caregiver on ART	65 (100)	36 (97)	-	*0.183*
Caregivers age > 30years	73 (64)	49(39.2)	1.6(0.9-2.9)	*0.122*
Caregivers had Secondary education	81 (71)	45 (61)	1.6(0.9-2.9)	*0.144*
Caregiver employed	75 (66)	42 (57)	1.5(0.8-2.7)	*0.212*

We evaluated the effects of different caregiver characteristics on adherence in a univariate analysis as shown in table 7 above. In this analysis, adherence was not found to correlate with the following caregiver characteristics: age, knowledge of their own HIV status, being on ART, having education up to secondary school or being in employment.

Table 10: Correlation of child characteristics to adherence by pharmacy pill count

Child characteristics	Good adherence Frequency (%) n=114	Poor adherence Frequency (%) n=74	Odds Ratio (95% CI)	P
Sex (Male)	53 (46)	41 (55)	0.7(0.4-1.3)	0.232
Age ≥ 6 years	66 (58)	32 (43)	1.8(1-3.3)	**0.049**
Child Knows his/her HIV Status	14 (12)	5 (7)	1.9(0.7-5.6)	0.220
Both parents alive	100 (88)	71 (96)	0.3(0.1-1.1)	0.055
WHO Stage I & II at time of ART initiation	30 (26)	19 (26)	1.0(0.5-2.0)	0.922
≥300cells/ul at initiation of therapy*	65 (57)	55 (74)	0.5(0.2-0.9)	**0.016**
Nutritional supplements given	27 (24)	16 (22)	1.1(0.6-2.30	0.743

*300 cells/*ul* was the median CD4 cell count at initiation of therapy.

The effects of different child characteristics on adherence were evaluated in univariate analysis. We found that the child being older (≥ 6 years) had a positive effect on adherence while having a CD4 count of more than 300cell/ul at initiation of therapy had a negative effect on adherence. There was also a trend, with children who had both parents alive having a higher likelihood of being non-adherent. Adherence was not found to correlate with the following child characteristics: gender, child's knowledge of their HIV status, or being on nutritional supplements. This is shown in table 10 above.

MULTIVARIATE ANALYSIS

Table 11: Logistic regression for predictors of adherence by pharmacy pill count

Characteristic	Parameter Estimates	SE	95%CI	*P*
Child's age	0.96	0.05	0.87-1.1	*0.464*
Absolute CD4 counts	1	0.01	1.0-0.02	***0.096***

When child variables that were found to be significant in the univariate analysis were considered in the multivariate analysis, there was a trend, with the child having higher CD4 counts at initiation of therapy being associated with poor adherence. In the analysis, the child's age was not associated with adherence.

DISCUSSION

Our study on adherence to antiretroviral therapy in a routine paediatric comprehensive care clinic found that caregiver report gave higher adherence rates (87 %) compared to pharmacy pill count (61%). These levels of adherence are similar to those found by Arnsten et al, who compared electronically monitored adherence (MEMS) with self reported adherence in adult drug users. In this study, Arnsten found a mean self reported one-week adherence of 78 % and a mean MEMS 1 week adherence of 53%[6] We found a 26 % difference in the adherence levels between the two measures which is higher than that found by Farley et al in a study on children where he compared pharmacy pill counts and self-report and found adherence rates of 92 %, and 100 % respectively.[22]

Our study identified about four times more children as non-adherent by pharmacy pill count compared to self-report. This is higher than the aforementioned study by Fairley et al, on adults in Australia, where pharmacy pill count records identified about twice as many individuals as non-adherent compared to self- report, 27 % and 14.5 % respectively ($p=0.001$).[27] The reported adherence levels by use of 2 week recall that we obtained are similar to adherence levels from studies by Puthanakit et al in Thailand and Reddi et al in South Africa, who found reported adherence levels of 86 % and 89 % respectively by use of 2 week recall.[9,15]

Several other studies have also shown that self-report tends to overestimate adherence by about 5-20% when compared to adherence rates derived from more objective methods like MEMS and pharmacy records.[6,26,28]

In our study, the higher levels of reported adherence by use of 2 week recall could have been because face-to-face interviews are quite subjective and the caregivers may report what they feel is socially acceptable to the clinician. Also the caregiver may not feel free to tell the clinician the truth about missed doses if they are aware of the consequences of reporting non-adherence, which may include stopping of the medication. Another possibility is that because the effects of non-adherence may not occur immediately, some patients may not understand the consequences of not reporting the truth to the clinician and this may cause them to report to the clinician what appears desirable.

When we compared the two measures, we found that pharmacy pill count produced lower estimates of adherence than self report, as has been demonstrated in other studies. For example, Watson et al obtained adherence levels of 58% were in a retrospective study of adherence in children using pharmacy records.[23]The lower pharmacy levels could be closer to the reality in terms of adherence than the caregiver report. This is because the patients/caregivers may not view pharmacy pill count as a method used to gauge how they have performed in terms of taking their medicines since the pharmacist may appear to count the pills in order to determine how much medicine to dispense.

However, it may not be possible to state where the pharmacy pill count and self-reported adherence rates in our study fall in terms of true adherence. This is because the two measures of adherence did not correlate with the patients' clinical and immunologic improvement.

However the reason why we did not find any possible associations between the adherence rates and patient clinical response may have been because this study's sample size did not give it the power to determine the associations between the adherence levels and the patients clinical response. However despite this limitation, after 6 months of ART, pharmacy pill count performed better where adherent children by pharmacy pill count had a significant increase in WAZ-scores compared to non-adherent ones while the same was not observed with self-report. The possibility that self-report overestimates adherence may partly explain why there was no improvent in WAZ-scores amongst those children good adherence after 6 months of ART.

There was no major difference in reported adherence when we used 3 day recall (88%) and two week recall (87%). These findings are similar to a study by Arnsten et al on adults, whose aim was to determine if adherence does change over time. In this study on adults, patients were interviewed once every month both for 1 day and 1-week adherence information. The reported adherence levels in the 6 study visits did not differ significantly ($p=0.1$). In the same study, one-day and 1-week adherence estimates did not differ significantly either, 79% and 78% respectively ($p=0.14$).[6] There have been thoughts that self report can only be used to reflect recent behavior because it may be difficult to recall missed doses beyond short periods of time. However, our findings suggests that assessment of adherence for the immediate period preceding the clinic visit, or over a relatively short period may provide an efficient and reliable measure of adherence and this can give insight to adherence levels in the past.

Similarly, our study found similar levels of adherence over a one-month period (61%) compared to a longer period of six months (58%) by pharmacy pill count. This may imply that even if adherence was estimated using the one-month prior to the clinic visit, this may indeed guide the clinician about the patients' level of adherence over a much longer period of 6 months.

In our study, caregiver characteristics did not influence adherence. This is in contrast to a study by Reddi et al on children in Kwa-zulu natal South Africa. In this study, the primary caregiver being HIV infected or the caregiver being on ART had a positive effect on adherence[9].

We found a trend to children who were not orphaned being likely to be non-adherent. This is in contrast to a study carried out in Western Kenya which showed that adherence was not different between the orphaned and non-orphaned children.[34] A possible explanation could be that the non orphaned children live with their possibly HIV infected parents. Some of these parents may be too sick to administer medication to their children effectively. On the other hand, these findings may possibly suggest that the extended families of the orphaned children may be functioning relatively well allowing family members to give adequate support in the typical African culture that cherishes extended family relations.

We found a trend, whereby the child having better CD4 counts at initiation of ART was associated with non-adherence.

The reason for this could have been that the child who started ART with a worse immune status was more sick, prompting the caregiver to be more keen on administering the medication to the child compared to the relatively well child.

However we did not find a significant association between adherence and the following child characteristics: age, gender, child's knowledge of their HIV status or being on nutritional supplements. These findings are similar to those by Van dyke et al in the PACTG study.[21] These findings may be because children mainly depend on the caregiver for medication administration and support.

There were several limitations in our study. Considering that some of the liquid medicine may spill during administration, the actual pharmacy adherence may actually be lower than what we obtained. Also estimation of liquid formulations is a challenge and may not have been accurate due to inter-observer error. In the pharmacy, patients are required to bring back all the remaining doses and sometimes they forget or they may leave out excess doses intentionally therefore masking non-adherence.

While collecting information on reported adherence, some of the caregivers present may not have been the ones that routinely administer drugs to the child and this may have confounded the accuracy of information obtained. Also we were not able to access viral loads in these children because they are not done routinely in the clinic yet viral loads have been shown to be a reliable marker of adherence.

CONCLUSIONS

1. The two measures of adherence, pharmacy pill count and caregiver/self report yielded different results with self report giving higher adherence rates (87%) compared to pharmacy pill counts (61%).

2. Patients who were adherent by pharmacy pill count had a greater increase in WAZ score after 6 months of ART. There was however no difference in the other clinical and immunologic responses when patients were classified as adherent and non-adherent by either pharmacy pill count and self report.

3. There was a trend, with patients who had higher CD4 counts at initiation of ART being more likely to be non-adherent. How ever the other caregiver and child sociodemographic and clinical characteristics did not influence adherence.

RECOMMENDATION

1. These results suggest that there is need to incorporate pharmacy pill count as a method of adherence assessment during the routine clinical care of HIV-infected children at the KNH paediatric CCC.

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APPENDIX 1

CONSENT FORM FOR STUDY PARTICIPATION

Dr. Ng'eno of the Department of Paediatrics, University of Nairobi is conducting a study at the Comprehensive Care Clinic to find out, the reliability of the measurements clinicians use to monitor how your child takes their medicines.

I realize that taking pills every day is challenging. Actually most people have problems taking their medicine at some point during treatment. The reason I would like to find out how your child takes the medicine is because missing more than 5% of the doses in a month (e.g., more than 3 doses a month in a twice-daily regimen) can lead to the medicines not working well anymore. Missing less than this would be a good goal.

Feel comfortable to tell me about any medicines that may have been missed.

The information obtained from this study will assist us as clinicians to understand some of the challenges you undergo while giving these medicines to the child. As a result we will be able to work out a way of overcoming these challenges.

I would therefore like to offer you and your child the opportunity to be part of this study.

Study procedures

If you consent to participate in this study, I will then ask you questions related to you and your child's health. I will also ask you how your child has been taking medicines as well as your experiences on giving the medicine to your child.

After asking you questions, I will then perform a physical examination on your child.

If your child has been on treatment for six months and does not have current levels of CD4 counts, I will then take two milliliters of blood from the child, which will be used to measure CD4 counts and CD4 percentages.

Risks

Some of the questions I will ask might be personal. Also discussing your HIV status and that of your child might cause you some anxiety, but you need not feel obliged to answer any questions, with which you are uncomfortable, and this will not affect the child's management in any way. The needle puncture to draw blood for CD4 counts may cause pain to the child causing him/her to cry.

Benefits

During the child's physical examination, any new findings will be relayed to the clinic doctors so that he/she can give treatment. Even if your child does not directly benefit from this study today, you will know that information obtained from this study will help your child and other children in the future.

Cost

If your child needs a CD4 count test, this will be done at no cost to you, and no money will be paid to you for taking part in this study.

Confidentiality

The information you give during the interview and the results of the study will be held in the strictest confidence. They will only be shared with the clinic doctor if found necessary for the benefit of the child in terms of treatment and care. All study records will be stored in a locked room with a limited access restricted to the study personnel. Computer databases containing subjects information will be pass word protected and accessible only to study personnel.

Reassurance

You may opt not to participate in this study and the management of your child in the clinic will in no way be interfered with. If you decide to participate in this study, you may withdraw at any time during the interview without explanation or consequence.

To indicate that you understand the conditions of this study and that you consent to participate in it, please sign or put your thumbprint in the space provided below.

I.....Confirm that the study has been explained to me and I give consent to participate in it.

Signature/thumb print.....

Witness:

Name .....

Signature.....

Any clarifications regarding this study may be sought from;

(a) Principal investigator; Dr. Ng'eno Bernadette
P.O. Box 43777, 00100,
Nairobi
Tel No: 0737 777807, 0722 777807

(b) KNH ETHICAL REVIEW COMMITTEE
C/o Dr. Guantai
P.O.Box 20723
Nairobi

APPENDIX 2

QUESTIONAIRE

1. Child information

Social and family information

Date_____ OP No. _____ PEPFAR No. _____

Study number _____

1. Age ____years

2. Sex: ☐ Male ☐ Female

Factors influencing adherence

1. (a) Are the child's parents alive? No ☐ Yes ☐

(b) If yes, who is alive? ☐ Mother ☐ Father ☐ Both parents

(c) Do they live with the child? ☐ Yes ☐ No

2. Who brought the child to the clinic today?

☐ Mother

☐ Father

☐ Grandmother (paternal)

☐ Grandmother (maternal)

☐ Auntie (maternal)

☐ Child him/herself

Others, specify _____

3. Who brought the child to the clinic on the last visit?

☐ Same caregiver

Other persons, specify_____

4. Who is responsible for giving the child medicine?

☐ The primary caregiver

☐ The child

☐ Other, specify_____

5. (a) Does the child go to school? Yes ☐ No ☐

(b) If yes; primary school.....yrs

Secondary school.....yrs

6. (a) Does the child know his/her HIV status? Yes ☐ No ☐

(b) If yes, when did the child know about his/her HIV status? _____Months ago

(c) Who disclosed the status to the child?

☐ Caregiver

☐ Clinician

☐ Other, specify_____

(d) Who else knows about the child's HIV status?

☐ Mother

☐ Father

☐ Grandmother (paternal)

☐ Grandmother (maternal)

Others, specify_____

7. (a) Is the child taking food supplements (enriched porridge)? ☐ Yes ☐ No

(b) If yes when did he/she start taking supplements? _____ Months ago.

8. How long has the child been on antiretroviral therapy now? _____Months

ADHERENCE INFORMATION

1. Record the HAART regimen that the child has received since the last visit (let the caregiver show the box or bottle of medicines and state how much medicine they give the child per dose and the frequency per day).

ARV Combination	Amount of medicine given /dose		Number of doses / day Tick (√) to indicate		
	Liquid / syrup	Pills/capsules	Once	Twice	I don't know

2. Has the child missed doses of medicine in the last two weeks? Yes ☐ No ☐

3. Has the child missed any doses of medicine in the past 3 days? Yes ☐ No ☐

4. (a) Last time the child missed a dose; did the missed dose include all the drugs or specific drug(s)?

- ☐ Missed all three drugs
- ☐ Missed specific drug(s)
- ☐ N/A

(b) Specify the drugs missed and number of doses missed in the past 3 days.

Drugs missed	Number of doses missed

(c) Specify the drugs missed and number of doses missed in the past 2 weeks.

Drugs missed	Number of doses missed

5. If any dose of antiretroviral drug was missed, what led to the dose(s) being missed?

- ☐ I Forgot
- ☐ Child vomits on taking the medicine
- ☐ Side effects of medicines
- ☐ Drugs got finished
- ☐ Changed daily routine
- ☐ Fear that some one may find out child's HIV condition
- ☐ Medicine tastes bad, child spits out
- ☐ Others, specify _____

Child history of opportunistic infections

1. (a) Is the child ill today? ☐ Yes ☐ No

(b) Tick any complaint mentioned and indicate duration (in days)

- ☐ Cough _____days
- ☐ Difficulty breathing _____days
- ☐ Fever _____days
- ☐ Irritability _____days
- ☐ Difficulty breathing _____days
- ☐ Diarrhea _____days

Others (specify)_____

2. (a)In the last 6 months has the child been to hospital due to illness? Yes ☐ No ☐

(b) If yes, what was the problem? _____

3. (a) Has the child been hospitalized in the last 6 months? Yes ☐ No ☐

(b) If yes, for how long _____

4. What was the reason for hospitalization? _____

Child Physical examination

1. **General**

Body Temperature ____°c

Respiratory rate _____ /min

Heart rate _____min

2. Immunological stage (CDC)

	At HAART initiation	6 months ago	Current stage
Date			
Stage/CD4 %			

Caregiver Sociodemographic information

1. Sex: ☐ Male ☐ Female

2. Age _____ years

3. Area of residence_____

4. Education: number of completed years from standard one _____ years.

5. Occupation: ☐ Employed ☐ Unemployed

6. Income: Kes per month_____

Caregiver medical information

1. (a) Have you ever taken an HIV test? Yes ☐ No ☐

(b) If yes, do you know your HIV result? Yes ☐ No ☐

(c) What was your HIV result? HIV Positive ☐ HIV negative ☐

(c) If you are HIV positive have you been assessed to determine whether you need treatment? Yes ☐ No ☐

(d) If yes do you require treatment? Yes ☐ No ☐

(e) If yes above, are you on ART? Yes ☐ No ☐

(f) If yes for how long have you been on treatment? _____months

APPENDIX 3

ANTHROPOMETRY DATA ABSTRACTION FORM

Months	Baseline (at ART initiation)	M6	M12	M18
Dates *dd/mm/yy*				
Weight (kgs)				
Height (cms)				
WAZ-score				
HAzscore				
WH Z-score				

APPENDIX 4

LAB DATA ABSTRACTION FORM (CD4 COUNTS)

Months	Baseline	M6	M12	M18
Date_____				
CD4 cells/μ				
CD4 %				

APPENDIX 5

Immunological Classification Based on CD4 Count and CD4 percent.

(Revised version, WHO 2006)

Immune Category	Age related CD4 Values (%) / CD4 cell/µl			
	< 12 mo (%)	12-35 mo (%)	36-59 mo (%)	≥ 5 yrs (cells/mm^3)
Not significant	> 35	> 30	> 25	> 500
Mild immunosuppression	30-35	25-30	20-25	350 - 499
Advanced immunosuppression	25-30	20-25	15-20	200 -349
Severe immunosuppression	< 25	< 20	< 15	<200 or < 15 %

APPENDIX 6

WHO Paediatric Clinical Staging of HIV/AIDS Disease

Clinical Stage of HIV	Clinical events or condition
Stage 1	• Asymptomatic • Persistent generalized lymphadenopathy (PGL)
Stage 2	• Unexplained persistent hepatosplenomeqaly of body area or disfiguring • Extensive wart virus infection; facial, more than 5% of body area or disfiguring • Papular pruritic eruptions • Extensive HPV or molluscum contagiosum(>5% of body area / face) • Recurrent oral ulcerations(>2 episodes/6 mos) • Unexplained persistent parotid enlargement • Lineal gingival erythema • Herpes zoster • Recurrent or chronic upper respiratory tract infections : otitis media, otorrhoea, sinusitis, tonsillitis(>2 episodes/6 mos) • Fungal nail infections
Stage 3	• Unexplained moderate malnutrition (-2SD or Z score) not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 375°C, intermittent or constant ,>1 month) • Persistent oral candidiasis (outside 6-8 weeks of life) • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis/periodontitis • Lymph node TB • Pulmonary Tuberculosis • Severe recurrent presumed bacterial pneumonia (current episode plus 1 or >in the previous six months) • Symptomatic lymphoid interstitial pneumonitis (LIP) • Chronic HIV-associated lung disease including bronchiectasis • Unexplained anaemia (<8gm/dl). Neutropenia (1,000/mm^3), or thrombocytopenia (<50000/mm^3) for >1mo. •
WHO Paediatric Presumptive Clinical stage 4 (age <18 months)	• For a symptomatic HIV antibody positive infant age <18 mos make a presumptive diagnosis of severe HIV disease (clinical stage 4) when: (a) Two of the following are present: oral candidiasis/thrush severe pneumonia sepsis OR (b) Diagnosis of any AIDS indicator condition(s) can be made (see below) Other supporting evidence: Recent HIV- related maternal death or advanced HIV disease in the mother ; and/or CD4 <20%

Stage 4	• Unexplained severe wasting or severe malnutrition (-3SD, as defined by WHO IMCI guidelines) not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe presumed bacterial infections e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia (current episodes plus ≥1 in previous 6 months • Chronic orolabial , cutaneous, or visceral (any site) HSV infection (lasting >1 month) • Extrapulmonary TB • Kaposis sarcoma • Oesophageal candidiasis (or Candida of trachea, bronchi or lungs) • Central nervous system toxoplasmosis (after the neonatal period) • HIIV- related cardiomyopathy • HIV-related nephropathy • HIV encephalopathy • Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month • Extrapulmonary cryptococcosis (including meningitis) • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis, penicillinosis) • Cryptosporidiosis or isosporiasis (with diarrhoea >1 month) • CMV retinitis or infection affecting another organ , with onset at age >1 month • Disseminated mycobacteria infection other than tuberculosis • Acquired HIV-associated rectal fistula • Cerebral or B cell non-Hodgkin lymphoma • Progressive multifocal leukoencephalopathy (PML)

ARV Drug Information Entry/View

DATE: 09-Mar-05

Patient ID No: TEST 01

First Name: JOSEPHINE THITU

Surname: MAUNDU

Child (<= 15 yrs) ☑ Adult (> 15 yrs) ☐

Sex: MALE Pregnant? ☐

	Start	Current
Age (yrs)	12	
Wgt (kg):	35	38
BSA (msq)	1.23	1.35

Date Approved: 09-Sep-03 Show

Date Started: 01-Jan-04 Show

Source of Patient: OUT PATIENT

Supported By: GOK/NASCOP

Type of Service: ART

Days to Next Appt: 30

Date of Next Appt: 20-Mar-05

Address: ACK GARDEN HOUSE WING A
FIRST AVENUE, NGONG ROAD OFF
BISHOPS ROAD. OFFICE NUMBER

Current Status: Active

Other Disease Conditions: TB (01-06-2002), ART TREAT

Other Drugs: METFORMIN 500MG BD

ADR / Side Effects: rash to nvp

Reasons for Changes:

ART Status at Start: ☑ Naive ☐ Non-naive

Regimen: Start AR1

Current AR3

List of Drugs Dispensed

Date	Purpose of Visit	Drug Code	Unit	Brand Name	Dose	Duration	Quantity	Regimen	Comment
06-Dec-04	Start	d4T 30mg		Zerit	180	28	56	AR1	
06-Dec-04	Start	3TC 150mg		Epivir	180	28	56	AR1	
06-Dec-04	Start	NVP 200mg		Viramune	OD	14	1	AR1	
16-Dec-04	Switch Regimen	d4T 30mg		Zerit	180	28	56	AR2	
16-Dec-04	Switch Regimen	3TC 150mg		Epivir	180	28	56	AR2	
16-Dec-04	Switch Regimen	EFV 600mg		Stocrin	100	28	28	AR2	
30-Dec-04	Switch Regimen	ddi 200mg		Videx	180	28	56	AR3	
30-Dec-04	Switch Regimen	3TC 150mg		Epivir	180	28	56	AR3	

First Patient | Prev Patient | Next Patient | Last Patient | Find Patient | Save Patient | New Patient

APPENDIX 8

PHARMACY DATA ABSTRACTION FORM

	Quantities of doses of drugs prescribed and dispensed					
Drugs	**1.**		**2.**		**3.**	
	No. of doses dispensed	No. of doses prescribed	No. of doses dispensed	No. of doses prescribed	No. of doses dispensed	No. of doses prescribed
Month 1 (1st refill) date -------						
Mean adherence rate						
Month 2 (2nd refill) Date----------						
Mean adherence rate						
Month 3 (3rd refill) Date.....						
Mean adherence rate						
Month 4 (4th refill) Date.....						
Mean adherence rate						
Month 5 (5th refill) Date.....						
Mean adherence rate						
Month 6 (6th refill) Date.....						
Mean adherence rate over 6 mo per drug						

a) Mean adherence rate over one month (month 1) _____ %

b) Overall mean adherence rate over 6 months_____%

KENYATTA NATIONAL HOSPITAL
Hospital Rd. along, Ngong Rd.
P.O. Box 20723, Nairobi.
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

29th October 2007

Ref: KNH-ERC/ 01/ 4885

31/10/07
CCC Manager
to facilitate

Dr.Bernadette Ng'eno
Dept. of Pediatrics & Child Health
School of Medicine
University of Nairobi

Dear Dr. Ng'eno

RESEARCH PROPOSAL: "A COMPARISON OF SELF-REPORT AND PHARMACY PILL COUNT AS MEASURES OF ADHERENCE TO FIRST LINE ANTIRETROVIRAL THERAPY FOR CHILDREN WITH HIV-1 INFECTION IN A ROUTINE CLINIC AT K.N.H" (P270/9/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 29th October 2007 – 28th October 2008.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N'GUANTAI
SECRETARY, KNH-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Pediatrics & Child Health, UON
Supervisors: Prof. Ruth Nduati, Dept. of Pediatrics, UON
Dr. Dalton Wamalwa, Dept. of Pediatrics, UON