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

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### Abstract

Achieving optimal adherence to ARV's in a rural paediatric population is challenging. Monitoring adherence by frequent viral load assay is not always feasible or sustainable in rural communities. A relatively cheaper, reliable, valid and sustainable measure of adherence for children is required for routine management. This study retrospectively assessed adherence outcomes using monthly pill count and viral load data, including reasons reported for non-adherence, in a paediatric cohort in rural KwaZulu-Natal, South Africa. Between 2008 and 2013, 78 children, mean age of 7.1 years, were enrolled in the CAPRISA 052 AIDS Treatment Programme. Monthly treatment adherence by pill count was categorized as either high (≥95%) or low (<95%). Overall median monthly adherence to treatment by pill count was 87.8% at month six, 88.9% at month 12 and 90.8% at month 24. However, the proportion of children with an undetectable viral load (< 400 copies/ml) was 84.0% (63/74), 86.6% (58/67), and 84.5% (49/58) at the three time points respectively. Agreement between pill count and viral load showed that only 33.9%, 36.3% and 30.6% of children were truly adherent by pill count at months six, 12 and 24 respectively. In conclusion, this treatment programme demonstrated that adherence of >95% by pill count is not an ideal indicator of virological suppression in children aged six months – 13 years. Viral load assessment remains the gold standard for assessing treatment success in this age group.

### Keywords

Paediatric; Children; Adherence; Rural; ARVs

## INTRODUCTION

According to the World Health Organisation (WHO) in 2014, 2.6 million children (<15 years) were living with Human Immunodeficiency Virus (HIV) globally, 220 000 children

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### CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest

were newly infected with HIV and 150 000 children demised due to Acquired Immune Deficiency Syndrome (AIDS)-related illnesses (1). Sub-Saharan Africa remains the region with the highest number of children living with HIV, with a documented 2.3 million children living with HIV in 2014, and only 30% of these children (age 0 – 14 years) accessing antiretroviral treatment (ART) (2). In South Africa, of the 360 000 reported HIV infected from 2013 statistics (3), only 156 700 were initiated on ART (4).

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

Although comprehensive treatment guidelines are available in South Africa, achieving optimal adherence to ART (>95% of doses per month ingested) and maintaining virological suppression in a paediatric cohort remains challenging. With viral load assessed every six months or annually as per the National Department of Health Paediatric HIV Treatment Guidelines (13), the emphasis on finding an alternate interim (between viral load monitoring) adherence monitoring tool, particularly in rural areas, is indispensable. There is a paucity of information and insufficient guidance on how to measure and improve adherence in South Africa for this population.

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

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

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

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

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

## METHODS

### Study design, setting and participants

This was a retrospective analysis of routinely collected data from a paediatric cohort within the Centre for the AIDS Programme of Research in South Africa (CAPRISA) 052 AIDS Treatment programme, for the period June 2008 to September 2013. Located in the uMgungundlovu district in rural KwaZulu-Natal, South Africa, this district is one of six in South Africa with an alarming HIV prevalence of >40% in antenatal care attendees (23).

The paediatric treatment programme, funded by the President's Emergency Plan for AIDS Relief (PEPFAR), offered programmatic HIV care to children below the age of 15 years in accordance with the South African National paediatric treatment guidelines used at the time. Children were eligible to start treatment if they met the following inclusion criteria: Recurrent hospitalisations for HIV-related disease or WHO stage 2 / 3 disease, CD4 percentage < 20 for those children <18 months or CD4 percentage <15 for those children 18 months. The children enrolled into the treatment programme were either ARV naïve, ART treatment interrupted requiring ART re-initiation, or requiring treatment continuation after transfer in from surrounding local clinics.

Tools such as 7-day pillboxes allowing twice-daily drug storage and cell phone alarm reminders were introduced in an attempt to improve adherence. Reminders generally coincided with a daily activity like the start of a popular television programme or brushing of teeth in the morning. Pharmacy staff assisted caregivers and children with packing the weekly pill boxes, labelling the daily or twice daily pill boxes with sun / moon pictograms,

and with setting a cell phone alarm reminder. At the next contact visit they were reminded to return the pill box together with any remaining medication still in bottles including left over liquid formulations.

### Data collection in CAPRISA 052

Data was collected on case report forms by healthcare workers during monthly visits to the clinic. Prior to the current analysis the database was reviewed, cleaned and missing or incompletely captured variables were imputed into the database. Baseline demographics collected at screening included age, gender, WHO staging, previous ART exposure, tuberculosis (TB) status and treatment history, CD4 count, viral load and the ART regimen they were enrolled on. The type of primary caregiver and parent status were also collected. Screening and enrolment visits included comprehensive counselling of the primary caregiver, emphasizing the reasons for starting ART, accentuating the importance of maintaining adherence, discussion of possible ARV side-effects, responsibility of the primary caregiver, and disclosure.

At every monthly visit, weight, height and TB status was documented. Blood samples were collected every 6 months to assess CD4 count, viral load, fasting cholesterol, liver function, glucose and triglycerides. Intense adherence support counselling was offered as needed to children and their caregivers when pharmacy adherence calculations by pill count was below 95%. Monthly adherence support counselling was offered as needed to children and their caregivers when pharmacy adherence calculations by pill count was below 95%. At this counselling session the staff member went back to basics, importance of adherence, and readiness for ART and provided primary caregiver support. Additional adherence counselling and support was provided if treatment failure was suspected. Treatment failure was defined as having a detectable viral load >1000 copies/ml, tested three months apart, despite good adherence. At this point, children were then switched to an appropriate second line regimen. In accordance with the South African National Department of Health (SA NDoH) Antiretroviral treatment guidelines in 2004, the limit of detection of viral load was 400 copies/ml. This was subsequently updated in March 2013, in accordance with available test standards, to 50 copies/ml. However, viral load data in this study assessed at months 6, 12 and 24 was based on the limit of detection of 400 copies/ml for consistency. Drug regimen changes and/or single drug switches, for virological failure or medication intolerance respectively, was assessed.

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

Caregiver or child self-report was used to ascertain reasons for missing doses (patient ran out of pills, clinic ran out of medicine, caregiver status changed, cannot recall, caregiver/patient forgot, caregiver did not supervise, felt too ill, cannot recall/denies missing a dose, unknown/remaining medication not returned at visit, or any other reason). For the purpose of this study, monthly adherence by pill count was categorized as high if more than or equal to 95% and low if below 95%. This routinely used adherence categorization is from previous literature providing evidence that this cut off point is suitable for predicting virological

suppression and good clinical outcomes for patients on ART (8-10). For children receiving syrups in their regimen, a 5% volume margin of error was allowed to accommodate challenges in administering syrups, wastage/spillage and possible incorrect dosing volume with doses administered orally dosing by syringe.

**Adherence percentage for syrup formulations was calculated as follows:**

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

**Adherence percentage for tablet formulations was calculated as follows:**

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

The denominator accounts for the time elapsed between clinic visits.

**Statistical Analysis**

Baseline characteristics were summarised using proportions, means or medians where appropriate. Sensitivity and specificity were calculated for pill count adherence (95% vs. <95%) using viral load (<400 vs. 400 copies/ml) as the gold standard. Sensitivity and specificity were calculated using the standard definition from a 2x2 table. Sensitivity was calculated by dividing number of patients with (viral load <400 copies/ml and adherence 95%) by number of patients with viral load <400 copies/ml. Specificity was calculated by dividing number of patients with (viral load 400 copies/ml and adherence < 95%) by number of patients with viral load 400 copies/ml.

McNemar's test for dependent samples was used to determine whether there was a difference in the proportion of high/low adherers when measured using pill count and viral load at month six, 12 and 24. To account for multiple measurements of each patient, generalised estimating equations (GEE) for a multivariate repeated measure logistic regression model was used to identify predictors associated with undetectable viral (<400 copies/ml) load over time. The variables included in the multivariate model were adherence by pill count (95% vs. <95%), age, gender, WHO stage, whether guardian was the recipient of any grant and primary caregiver status. All statistical tests were conducted at a 5% level of significance and analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina).

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

## RESULTS

### Baseline Demographics and clinical characteristics

For the period of June 2008 – September 2013, the CAPRISA 052 AIDS Treatment Programme screened a total of 117 children and enrolled 79 (<18 years at time of enrolment) in the programme with only 78 initiated on treatment. The age range for these patients was six months – 13 years. Baseline demographics and relevant clinical characteristics are shown in Table 1.

### Adherence by pill count

At programme enrolment and depending on age and weight, 54 children received formulations consisting of a combination of tablets and syrups, whilst 24 children received tablet only regimens. The proportion of children who achieved adherence 95% at month six, 12 and 24 was 32.3%, 35.8% and 34.5% respectively. Overall median monthly adherence was 87.8% (interquartile range (IQR): 71.0-99.6%) at month six, 88.9% (IQR: 77.1-99.8%) at month 12 and 90.8% (IQR: 79.1-99.2%) at month 24. Median monthly adherence by pill count remained above 85% throughout the follow up period (Figure 1).

### Reasons for missing doses

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

### Clinical Response to Antiretroviral Treatment

The proportion of children with an undetectable viral load (< 400 copies/ml) were 84.0% (63/74) at month six, 86.6% (58/67) at month 12, and 84.5% (49/58) at month 24. At the end of the follow-up period three children had died, one between month 0 and six of follow-up, and two between month six and 12 of follow-up. A total of 17 children were transferred out to their local primary health care clinics, during the 24 month period, for ongoing care (Figure 3). Reasons for transferring children out was mainly due to relocation of the family to other areas within the district.

During the two year follow-up period, five children were switched to second line treatment due to treatment failure. Treatment failure for four children was confirmed at their month 12 visit and one child experienced treatment failure at month 24. The overall median adherence for these 5 children at month six, 12 and 24 was 95.1%, 80.3% and 100% respectively. Viral load suppression was achieved after regimen change for all five children, however one child had a detectable viral load 11 months after the regimen switch due to non-adherence. Three other children had a single-drug switch on first line treatment due to laboratory / clinical toxicity (two were for hyperlactatemia and one for suspected abacavir allergy).

### Agreement between adherence by pill count and viral load

Sensitivity and specificity for adherence by pill count and viral load (gold standard) was low. We found that 33.9%, 36.2% and 30.6% of children with >95% adherence using pill count achieved viral load suppression at month six, 12 and 24 respectively (Table 2).

### Predictors of viral load suppression

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

## DISCUSSION

Our study found that overall adherence measured by pill count remained above 85% throughout a two year follow-up period and good clinical outcomes were achieved in this rural paediatric ART cohort. Children with an overall adherence  $\geq 95\%$  were nearly four times more likely to have an undetectable viral load. However, in our study, sensitivity of pill count to predict adherence by using viral load as a gold standard was very low and this may possibly be attributable to the  $\geq 95\%$  definition for high adherence. The sensitivity and specificity of adherence measures are significantly influenced by the cut-off points chosen by investigators to define the level of adherence (24). Although, the pill count is an excellent measure for healthcare workers to assess adherence more frequently (25), the gold standard for assessment of adherence to treatment remains the viral load measurement. This highlights the significant challenges in managing adherence on HIV treatment, where the outcome (viral load suppression) measured months after treatment initiation is indicative of therapeutic success or failure but a less invasive/expensive real-time measure to accurately monitor treatment remains elusive.

Pharmacy adherence measures such as returned pill count can play an important role in monitoring adherence (25), However studies suggest that multiple measures, and not pill count alone, should be used to predict adherence to maximize the reliability and validity of data collected (21, 26). This suggestion was strengthened by a study in New Jersey, USA that found an association between virologic response and the concordance of all three measurements of adherence: pharmacy refill, caregiver self-report and clinic appointment data (27). Similarly to us, other rural cohorts in Africa also found a positive association between medication return / pill count and viral load (15, 28). In addition the use of monthly pill count in our setting assisted in identifying adherence related barriers or challenges in between scheduled viral load monitoring bloods enabling these barriers to be addressed by referral for additional adherence support counselling.

Early literature suggested that adherence of 95% should be maintained for a patient to achieve virologic suppression and good clinical outcomes (9), and this percentage is often used in practice when assessing a patients' adherence. However, the association between adherence and virologic response in other studies is not always consistent (7, 10, 27). In our study the proportion of children achieving an undetectable viral load was similar to that of the children at the Sinikethemba Clinic, in rural Kwa-Zulu Natal where 84% of the children had an undetectable viral load at month six and 80.3% children had an undetectable viral load at month 12 (14). Of the children in a prospective cohort study in Cape Town 78% achieved undetectable viral load (15) and in Kigali, Rwanda, an undetectable viral load was attained for 82.8% children (29). In the Cape Town cohort the percentage of children achieving medication return adherence > 90% was 79%, and approximately 58% of the children achieved an adherence above >95% (15). Another prospective study in Uganda showed that over the 12 months of treatment about 40% of the children consistently had a detectable viral load (30). Alarming children from New Jersey had poor virologic response to ART with not even 40% of the children achieving an undetectable viral load of < 400 copies/ml (27). However, that study only used a single-point measurement for viral load to compare virologic outcomes with adherence. In our study, treatment failure and poor tolerance to ART resulting in drug switches was not common, with five children failing first line treatment and only three requiring a toxicity-related single drug switch.

An important predictor of having an undetectable viral load in the present study was having WHO stage 3 and 4 at baseline. Similarly, Ethiopian paediatric patients with baseline WHO stage 3 and 4 were more adherent to their treatment (31) as were children with WHO stage 2 or 3 in Cape Town (15). It is possible that disease severity positively impacts treatment adherence in paediatric patients. In contrast, a South American study demonstrated that experiencing a WHO stage 3 and 4 event during the course of treatment was positively associated with viral load > 5000 copies / ml (32).

Several factors may have played a role in the less than optimal adherence demonstrated by some children in our cohort. Some were on ART for longer periods than those in other studies (10) and treatment fatigue may have set in. Our adherence data was collected monthly or two monthly as opposed to 3-day and 7-day recall periods utilised in other studies which may be easier to remember (30, 33). Poor adherence by pill count can be influenced by errors in measuring and administering liquid formulations. Pill dumping in toilets or outside bins at the clinic has occurred in our setting albeit infrequently. Children have deliberately threw extra pills away before visiting the pharmacy in order to appear adherent – reported anecdotally by pharmacy staff.

It is important to take into account the influence of the primary caregiver on adherence. In a Cape Town cohort a high percentage (88%) of mothers were the primary caregiver (15) and both parents were alive for 72% of the Zambian children (28). In our cohort 42.9% of children have lost both their biological parents and about half of the cohort had a primary caregiver other than their biological parents. Our patients were more likely to have an undetectable viral load if the primary caregiver was not the biological parent. In contrast to our findings, a study in Elandsdoorn in rural South Africa reported that children who did not have a parent as the primary caregiver were more likely to have virologic failure (34). The



inconsistent results of the influence of the parent as the primary caregiver on adherence and virologic outcomes should be investigated. This highlights the importance of counsellors establishing supportive relationships with caregiver and child, in understanding the child's social circumstances, tailoring counselling messages and facilitating age-appropriate disclosure of the child's HIV status to empower them to eventually take full responsibility for their own health, understanding the implications of poor adherence. To maintain continuity of care a reliable secondary caregiver and handover of responsibilities to this individual when the primary caregiver is not available to support the child is crucial.

Studies have also shown that the socio-economic status of the caregiver is associated with poor adherence (14, 15, 35, 36). In our study children with caregivers who were the recipients of any social grant were more likely to have an undetectable viral load. Similar findings in USA, Zambia and Tanzania showed higher income levels and monthly household income were positively associated with viral load suppression (37-39).

Memory aids in our study consisted of weekly pillboxes and cell phone alarm reminders which were set to fit their daily routines. In an Ethiopian study the majority of caregivers (67.1%) reported that they were using their watches as a reminder (31). Children often did not like the pill boxes as they were concerned it would raise unwanted questions from friends and other family members. In a rural setting the availability of cell phones is limited and when the primary caregiver is not at home at the time when the child has to take the medication, doses could be missed.

In our programme forgetfulness of the primary caregiver and /or the paediatric patient was reported as the most common reason for non-adherence (31%), similar to other studies where forgetfulness by the caregiver was also distinctly recognised as a reason for non-adherence (19, 31, 33, 40). Other reasons for non-adherence that were similar to previous findings were that the child felt too ill to take medication, a change in daily routine or child ran out of medication (41, 42). In contrast to other studies, in our study side effects of antiretroviral medication reported as a reason for non-adherence was only 0.19% as compared to 16.3% and 4.3% in Ethiopian studies (41, 42) where side-effects of antiretroviral medication was found to be a predictor of adherence (38). In our treatment programme comprehensive counselling included discussing possible side-effects to expect and patients were advised to return to the clinic if any of these occurred for further management.

This study has several limitations. HIV disclosure and its correlation with adherence outcomes was not measured in our study. Pharmacy refill data as an adherence measure was not assessed. Not all medication was returned at each of the monthly visits as sometimes relatives were sent to collect medication and this may affect accuracy of the adherence assessment. Self-reported reasons for non-adherence are subject to recall bias and social desirability bias. In addition, all children and caregivers knew what to expect at the visit which included the pill count and questioning about any discrepancies. However, in a cross-sectional study in Ethiopia the proportion of children achieving an adherence >95% by pill count was similar to ours (34.8% vs. 35.8%) (31). The difference, between our assessment of adherence and that of the Ethiopian study is that we collected monthly adherence data

over 24 months, whereas their pill counts were unannounced and based on recall for the past seven days, but with very similar outcomes.

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

In conclusion, this treatment programme proved that relatively good adherence, with sustained adequate viral suppression up to 24 months follow up is attainable in a rural paediatric cohort in South-Africa. However, adherence of 95% by pill count is not an ideal indicator of treatment outcomes in HIV-infected children aged six months – 13 years. Viral load assessment remains the gold standard for assessment of treatment success in this age group.

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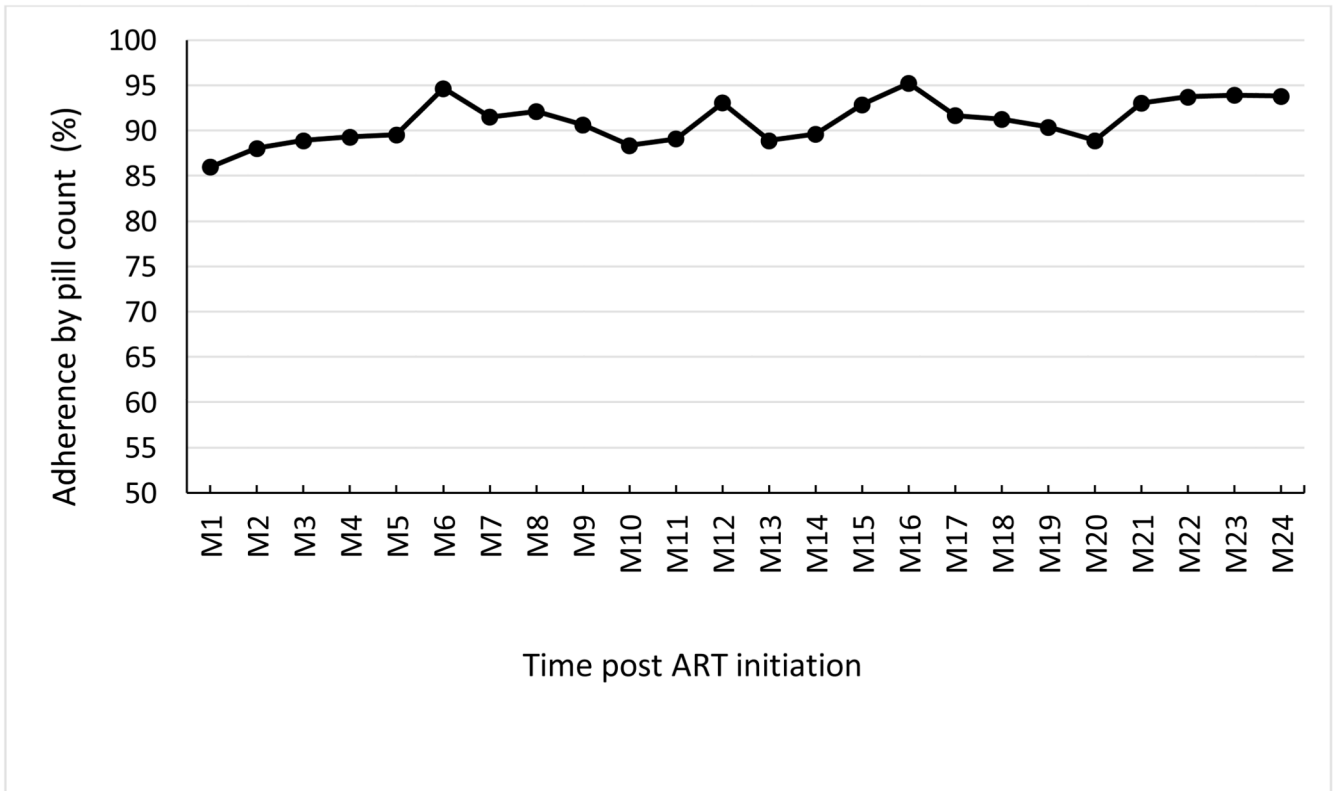


Figure 1. Median adherence over time

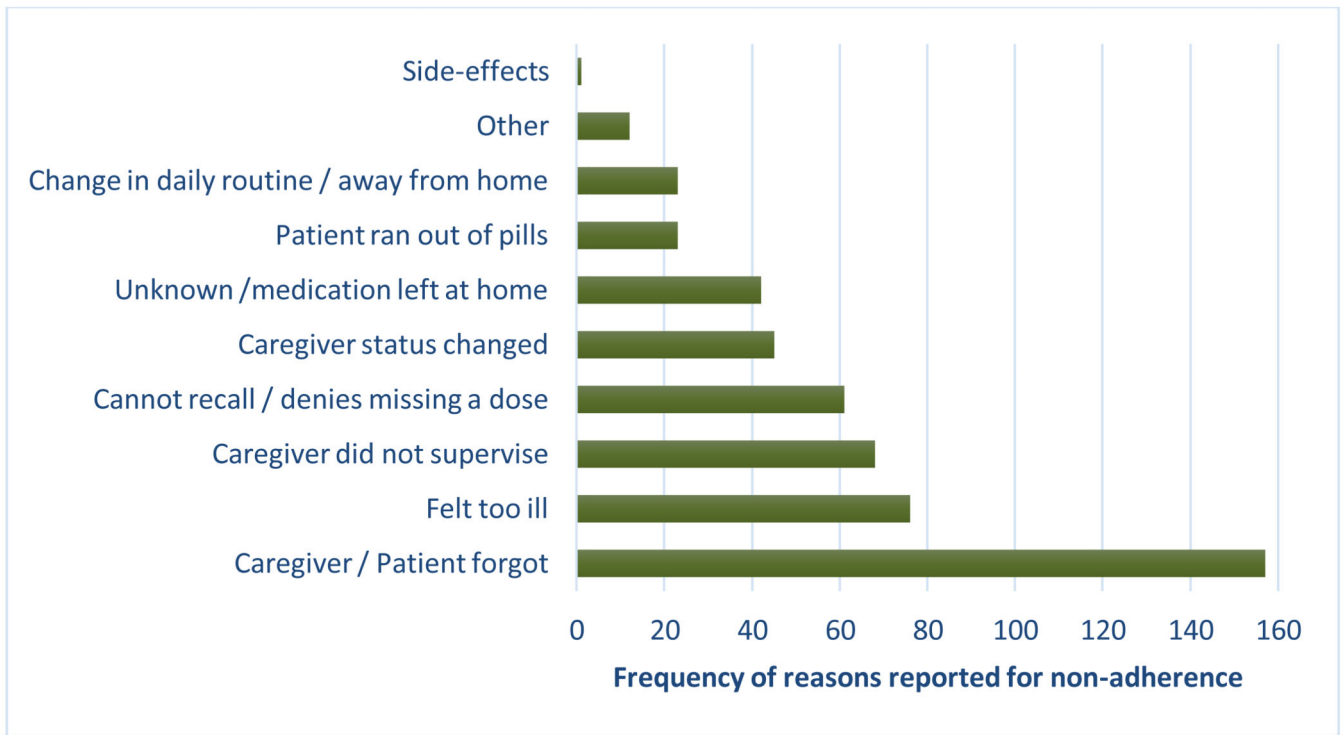


Figure 2. Frequency of reasons for missing doses reported for non-adherence

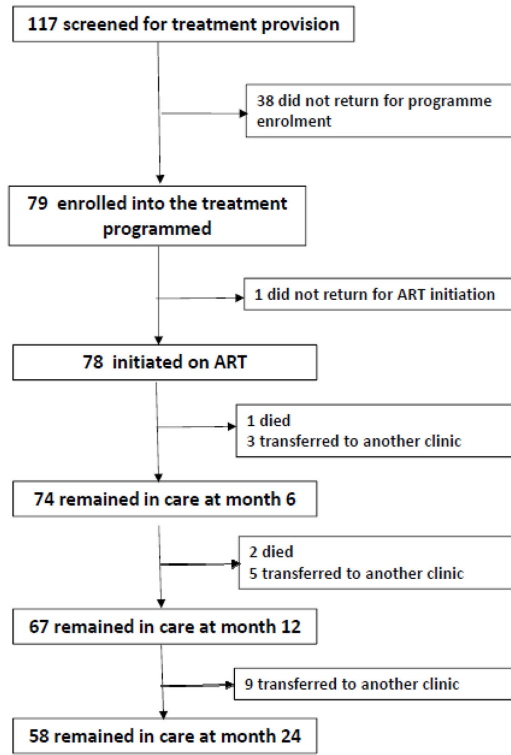


Figure 3. Patient outcomes in the CAPRISA 052 treatment programme

**Table I**  
**Baseline demographics and clinical characteristics**

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



Variable	Overall (N=79)
EFV/3TC/LPV/r HD	8.9 (7)

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

\*  
2 missing data

\*\*  
3 missing data

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

Adherence by pill count	Viral Load undetectable (<400 copies/ml)	Viral Load detectable (≥ 400 copies/ml)
<b>Month 6 viral load (N=74)</b>		
<b>95%</b>	21 (33.9%)	3 (25.0%)
<b>&lt;95%</b>	41 (66.1%)	9 (75.0%)
<i>Sensitivity</i>		33.9%
<i>Specificity</i>		75.0%
<b>Month 12 viral load (N=67)</b>		
<b>95%</b>	21 (36.2%)	3 (33.3%)
<b>&lt;95%</b>	37 (63.8%)	6 (66.7%)
<i>Sensitivity</i>		36.2%
<i>Specificity</i>		66.7%
<b>Month 24 viral load (N=55)*</b>		
<b>95%</b>	15 (30.6%)	4 (66.7%)
<b>&lt;95%</b>	34 (69.4%)	2 (33.3%)
<i>Sensitivity</i>		30.6%
<i>Specificity</i>		33.3%

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

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

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