

Barriers and Facilitators of Adherence to
Pediatric Antiretroviral Therapy Regimens
in Resource Limited Settings:
A Systematic Review and Qualitative Research Plan

By

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A Master's Paper submitted to the faculty of
the University of North Carolina at Chapel Hill
in partial fulfillment of the requirements for
the degree of Master of Public Health in
the Public Health Leadership Program.

Chapel Hill

2009

Summary:

Introduction: Good adherence to ART is known to be extremely important for successful suppression of HIV viral load and to improve clinical outcomes in children. However, high rates of adherence, greater than 95%, are needed to achieve these goals. Therefore it is important that clinical and support staff who work with caregivers and their HIV children understand the importance of good adherence and convey this message to their patients. To do this, we need a foundation of knowledge with which to base an adherence theory on and an understanding of the barriers and facilitators to ART adherence. Though much work on understanding ART adherence has been done in developed settings, the majority on adults, there continues to be a paucity of research and lack of guiding theory regarding ART adherence in children in resource limited settings. This is a significant problem, as the number of children living with HIV in resource limited settings continues to grow, especially in places like sub-Saharan Africa which accounts for 90% of all children living with HIV. Recent scale-up efforts of ART to children in resource limited settings means that adherence has become a highly salient issue. Studies to date on pediatric ART adherence in resource limited settings incorporate a wide array of study populations, study designs, adherence measurement strategies, and definitions of adherence. Drawing conclusions from these studies and development of a culturally appropriate adherence theory has been difficult. Prior studies recommend that more qualitative, formative research will be helpful in the development of such an adherence theory and to help inform the design of more uniform future studies.

Systematic Review:

Objectives: This paper includes a systematic review (Section II) of qualitative research assessing pediatric ART adherence in resource limited settings. The objective was to obtain a better understanding of what types of qualitative literature exist regarding ART adherence in children in resource limited settings, along with their contributions to the literature.

Methods: I searched online bibliographic databases, including MEDLINE, EMBASE, NLM, Cochrane Database, and various conference abstract databases using systematic criteria. Studies were selected for review that used qualitative methods to assess ART adherence in children less than 18 years of age in resource limited settings. The qualitative findings were extracted and summarized.

Results/Discussion: The review found 4 studies which incorporated qualitative methods and made an assessment of ART adherence in children in resource limited settings. Only 2 of the 4 studies were rated as 'good' quality and each differed in their methods and study populations. No pooled assessment of the results could be made due to the heterogeneity of studies. However, major themes which were commonly cited as barriers to adherence include poor caregiver-child relationships and structural barriers such as cost, access, and transportation. Common facilitators of adherence included having a support system for the child or caregiver and the development of an adherence strategy that both the child and caregiver can rely on. It is clear more such studies of high quality are needed to confirm the results of these studies and to add to our understanding of this topic.

Research Plan:

Objectives/Rationale: A research plan was developed to add to our general understanding of why ART regimens are difficult for children in resource limited settings (Section III). The objective of this plan was to inform more accurate measurement of adherence and the development of culturally appropriate best practice ART adherence guidelines. Since little data exists on adherence to pediatric ART regimens in resource limited settings, the Kalembe Lembe (KLL) Pediatric Hospital in Kinshasa, Democratic Republic of the Congo represents a prime target for farther study. Little information exists regarding adherence in Kinshasa. To date, direct assessment of pediatric adherence at KLL has yielded rates well above expected norms of children in similar settings and lack expected variability of adherence rates between subjects. Qualitative methods represent a sensible place to begin study in a new setting. They can be used to inform the development of more valid, culturally appropriate adherence measures and a contextual adherence theory, as well as provide more in-depth information than quantitative studies alone.

Methods: This plan called for a set of 40 qualitative interviews to be administered to HIV positive children taking ART regimens and their caregivers at the KLL Pediatric Hospital. An interview script for adults, HIV status disclosed children, and HIV status non-disclosed children were developed to assess barriers and facilitators to ART adherence in this setting. Demographic information were also collected. Interviewers were trained and interviews were recorded for transcription and translation into English. IRB approval was obtained and the project was begun in June of 2009. Analysis of results will take place following completion of the study.

Feasibility of Research Plan and Lessons Learned:

Experiences with implementation of research plan and lessons learned during this process are outlined in the last section (Section IV). Working in foreign settings can be quite challenging. Language barriers and the constraints of working in a resource limited setting were the most difficult aspects. International research requires a good understanding of the needs of a population in a given locale and a strong awareness of the infrastructure available to perform a particular study. To overcome such barriers, it requires good communication and collaboration with local colleagues. Planning for such projects should not be rushed. The timeframe and budgeting of such projects will likely require the most preparation. Overall, this research plan was feasible and the lessons learned in implementing this plan were valuable.

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I. Introduction

1. Background

General Overview:

There are over 2.1 million children world-wide living with HIV/AIDS.¹ With 370,000 new infections in 2007, this number is continuing to grow, especially in places like sub-Saharan Africa, which accounts for 90% of all children living with HIV.¹ Fortunately, over the past decade many low and middle income countries have made commitments to scale up antiretroviral therapy distribution to children. This is partly due to the World Health Organization's (WHO) '3x5' initiative and the Joint United Nations Program on HIV/AIDS (UNAIDS) initiatives for children, which has a goal to provide ART or cotrimoxazole prophylaxis therapy to at least 80% of children in need by 2010.

Progress has been made to increase availability of ART in these settings, thanks to increased advocacy along with the decreasing price of drugs and a focus on infrastructure for pediatric care. In 2007, nearly 200,000 children received ART in resource limited settings, compared with only 75,000 in 2005.² Within the past 5 years, the US President's Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis and Malaria, the Clinton Foundation, and the international drug purchase facility, have all made significant financial and technical contributions to scaling up pediatric HIV treatment.¹ This has allowed ART to reach children in even the most remote parts of the world.

The push for higher rates of pediatric ART stems from data that show treatment in both HIV positive adults and children can reduce viral load, significantly improve mortality rates, and can improve quality of life.²⁻⁵ In resource limited settings, ART has been shown repeatedly to improve clinical outcomes in children, including the initiation of early treatment in infants.^{2,6} Without access to ART, prognosis of HIV infected individuals is poor.⁷

Despite the improved availability of ART drugs, adherence remains a problem. ART regimens are complicated for children. While once a day combination dosing is available to adults and older adolescents in some resource limited settings, younger children are typically still on standard therapy with three different drugs. Syrups and solutions are necessary for treating infants and young children who cannot swallow pills. However, these have shortcomings, which may include limited availability, high cost, storage difficulties, reduced shelf-life, and alcohol excipient or solutions leading to poor palatability. Many other drugs do not have pharmacokinetic data on, or formulations suitable for, pediatric dosing.⁸ Often regimens may require up to 4 doses per day, making routine administration difficult. Fortunately, pediatric fixed dosed regimens and combination ART are becoming more widespread in resource limited settings.

ART Adherence in Children:

Accurately measuring ART adherence in children is extremely important, as it is critical to know the frequency of, and reasons behind, first line ART regimen failures. How often do these regimens fail? Further, is it because first line treatments develop resistance and have become ineffective in reducing viral load levels, or are failure rates due in large part to non-adherence of these medications? In the latter case, unnecessary switches to expensive alternate or second line regimens may occur, resulting in a failure to address the underlying problem. Without an understanding of true adherence rates and barriers to good adherence, addressing failure of treatment regimens in children becomes a difficult process.

It is known that high levels of ART adherence are required for successful treatment of HIV. Studies show that at least 90% to 95% adherence to ART regimens is needed for optimal virologic suppression and to minimize failure rates.⁹⁻¹¹ This level of adherence is recommended by the current pediatric ART guidelines in Africa.¹² In one highly cited study, 81% of those with >95% adherence recorded complete virologic suppression, compared with only 64% of those with 90-95% recorded adherence.¹⁰ Virologic suppression decreased significantly with

continuing decline of adherence rates. Without adequate adherence to ART, viral resistance, opportunistic infections and ultimately failure of therapy can result.¹³⁻¹⁵

Adequate adherence to pediatric ART regimens is possible in low and middle income countries.¹⁶ In some instances, adherence is equal to or better than rates in higher income countries, where children typically receive increased support and less complex regimens.¹⁶ However, in many instances adherence rates are still sub-optimal. Reported rates vary from as low as 49% adherence up to 100% adherence rates. In one well conducted systematic review of 17 articles assessing pediatric adherence in low and middle income countries, 13 articles reported >75% adherence rates in their study cohort, although only 5 reported ≥95% adherence.¹⁶ Given that 3 of those 5 studies reporting >95% adherence were patient or caregiver self reports of 100% adherence and did not employ any validation strategies on measurement, it is likely these are overestimates. This review and its findings are addressed in greater detail in the *Literature Review: Overview* section (Part I: Introduction, Section 2).

Accurate assessment of adherence in these settings is much more difficult without ready access to objective testing measures, such as viral load or CD4 counts. Though a number of low tech measurement techniques for ART adherence in resource limited settings exist, it is not known which are most reliable or accurate. Evidence suggests that more invasive techniques of measuring adherence tend to yield lower rates of adherence.¹⁷⁻¹⁹ For instance, studies implementing pill counts to determine adherence rates report lower rates than those where clinicians rely on self reported adherence rates during interviews or follow-up visits. Unannounced home pill counts and Medication Event Monitoring System (electronic measurement) yield even lower numbers.^{17, 19} This suggests that there is a significant recall bias or social desirability bias present when children and their caregivers are directly asked about medication regimens. Therefore, directly asking about adherence may not be an optimal strategy for the accurate measure of adherence.

Measurement of ART adherence is thought to be much more complex in children compared with adults, as good adherence often depends on many additional factors.^{16, 20} For instance, adherence factors in children can be extremely variable depending on age. Younger children will depend more heavily on the caregiver, whereas older children gain autonomy and become increasingly responsible for taking their own medication as they age.

Unfortunately, both younger children and older adolescents may not be aware of their HIV infection, and may not be well informed of the rationale behind taking such a complex regimen of medication. Estimates of HIV status disclosure to children in sub-Saharan Africa range from 75% to as low as 20%.²¹ Often caregivers who present to the clinics are not the primary care giver at home, making assessment and understanding of poor ART adherence during routine clinic visits challenging. Due to these complex issues there is little consensus on what underlying factors contribute most to pediatric ART adherence in resource limited settings.¹⁶

While numerous studies in adults have been undertaken to better understand adherence in these settings, studies in children have been sparse. To date, quantitative studies in children looking at factors predicative of non-adherence are variable in both their methods and results. Definitions for what is meant by 'adherent', factors measured, and analyses vary widely among published studies. At this time there appears to be a lack of guiding theory in pediatric ART adherence research and no reliable predictors of non-adherence have been established.^{16, 22-24}

Aims of the Paper:

Adherence to pediatric ART regimens has not been well characterized in resource limited settings. A better understanding of barriers and facilitators of adherence is needed to allow development of more accurate measures of adherence.

I will conduct a systematic literature review (Section II: Systematic Review) to determine what we understand about pediatric ART adherence, focusing on studies that incorporate qualitative methodologies. As I will describe in the next sections, the lack of guiding theory in

assessing pediatric ART adherence in resource limited settings justifies the need for a qualitative study.

This paper will also outline a research plan (Section III: Research Plan) for a qualitative research study incorporating in-depth, semi-structured interviews to assess pediatric ART adherence at the Kalembe Lembe Pediatric Hospital in Kinshasa, Democratic Republic of the Congo. During the course of the paper I will travel to Kinshasa and work to implement this research plan. Also, I will describe the feasibility of implementing qualitative research in resource limited settings and lessons learned during the experience (Section IV: Implementation of Research Plan and Lessons Learned).

It is the hope that information gathered from this systematic review and research plan will ultimately inform the design of future studies so we can continue to better understand, measure, and ultimately help provide best practice guidelines for improving pediatric ART adherence in Kinshasa and in other resource limited settings.

2. Literature Review:

Overview:

The majority of literature available on pediatric ART adherence in resource limited settings appears to exist in the form of quantitative studies that incorporate statistical methods to determine correlates to non-adherence. The most recent published systematic review on children over viewing this type of literature was completed by Vreeman and colleagues in 2007.¹⁶ Their study revealed 17 published studies on this topic. Their aim was to 'compile and critically analyze pediatric ART adherence measurement in resource limited settings to inform adherence monitoring strategies' and to provide 'measurement techniques, adherence estimates, and clinical correlates to inform ART adherence monitoring.

Their search strategy included MEDLINE, EMBASE, bibliographic searches and relevant websites, such as those of the WHO, United Nations Children's Fund, and the International AIDS Society covering dates from January 1st, 1966 to September 13th, 2007. Populations

assessed were children 18 years of age or less, though some studies also incorporated adults as study subjects. Countries included were those of low and middle income as defined by the World Bank.²⁵ All articles were in English and displayed a 'descriptive interventional study describing non-pregnant, HIV positive children that measured ART adherence'.¹⁶ No assessment of quality was undertaken for these studies, other than the initial inclusion criteria. They noted some studies were 'reasonably well done' while others 'did not have ideal methodological strength'.

Their results reveal studies on pediatric ART adherence in resource limited settings incorporate a wide array of study populations, study designs, adherence measurement strategies, and definitions of adherence. Strategies for measuring adherence within the studies included self or caregiver reports, pill counts, pharmacy records, clinic attendance, or serum drug levels. No studies used direct clinical indicators, such as CD4 count or viral load, to assess adherence, nor did they correlate adherence with direct clinical outcomes.

Definitions of 'adherent' varied among studies and prevented the authors from pooling results or conducting a meta-analysis of correlates to adherence. The definition used for 'adherent' is an especially important distinction in statistical analyses, where subjects must be defined as either adherent or non-adherent. Further, adherence rates were assessed over different time spans, ranging from 1 to 30 days.

Only 6 of the 17 studies within the Vreeman *et al.* review were specifically designed to identify predictors of non-adherence. General themes arose among the studies; however there were few consistencies among all 6 studies. To overview their findings, the studies reveal familial and social factors to be most predictive of non-adherence. These are living in rural settings, disorganized biologic families, low parental education, living in poverty, experiencing of stigma, and lack of caregiver availability. Reported instances of non-adherence included conflicts between the child and parent, having multiple adults involved in pill supervision, and

non-disclosure of the child's HIV status. Several of the studies also point out that complicated regimens, medication side effects, and high costs are also likely correlated with non-adherence.

Overall, Vreeman and colleagues conclude that due to the heterogeneity of the studies included in their review, it is difficult to draw any broad conclusions on best measurement techniques, best definition of 'adherent', best time frames in which to assess adherence, or predictive correlates to adherence. They also note that none of the studies reported any efforts to develop adherence measures using qualitative techniques to test these items and ensure cultural relevance and validity, nor do they confirm cross cultural validation of item translation.

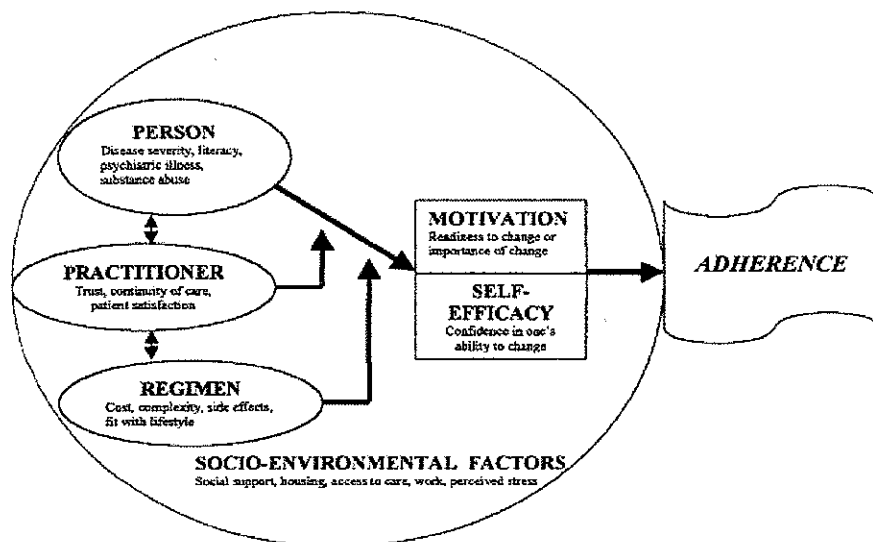
The review supports the notion that implementing systems to monitor pediatric ART adherence remains highly important. However, a comprehensive theory of pediatric ART adherence research is needed to guide future investigations of predictors of adherence. Vreeman recommends qualitative formative research will be useful in these settings to inform the development of more valid, culturally appropriate measures and a contextual adherence theory.

Since the Vreeman *et al.* review, few additional studies on pediatric adherence in resource limited settings have been published. One prospective cohort study from South Africa in 2008 used medication return (MR) to measure adherence, coupled with viral and immune responses to treatment.²⁰ This was assessed over a period of one year. 'Adherent' was defined as $\geq 90\%$ of medication taken (ie $< 10\%$ returned). The study found access to water and electricity as well as caregivers having secondary education or higher was associated with being adherent. Also, the MR method appeared to correlated well with viral load and CD4 count testing. In another study conducted in Togo from 2008, 'adherent' was defined as no caregiver reported missed doses in the past 4 days.²⁶ They found that female gender, living in an individual setting, receiving other than NNRTI-based regimen and caregivers' perceived difficulty of ART administration were associated with non-adherence.

There are several other studies similar studies published on children in resource limited settings. Though these studies do yield valuable information for their settings, they still face the same problems noted in the Vreeman *et al.* review. That is, heterogeneity of methods and variables measured, varying definitions of what is meant by 'adherent', and the clear heterogeneity of findings using logistic regression of dichotomous variables. This continues to support the assertion that an improved theory on pediatric adherence is needed to guide future, and more uniform, research.

There has been some work done on development of adherence theory in adults in the USA. Adamian *et al.*²⁷ worked to combine the more than 200 variables that have been used to assess and measure adherence in past studies and boil this down into simplified categories of factors relating to the person, practitioner, the regimen itself, and socio-environmental factors. They used 'social cognitive theory with empirical studies of ART adherence' to ultimately suggest that patients' adherence is affected by both their motivation and self-efficacy, or confidence in their ability, to take the medication. They developed a figure which takes into account these major categories, as seen in Figure 1.

Figure 1. Conceptual model of factors affecting adherence to antiretroviral therapy²⁷



Ware *et al.*²⁸ were able to take adherence theory and provide guidelines for application to resource limited settings. They introduce a heuristic schema for examining the validity of conceptual models of adherence, such as that of Adamian *et al.*, in these settings. They note that for an adherence model to be socially and culturally valid it must 'accurately and comprehensively represent the dynamics of adherence for a socially and/or culturally defined group.'²⁸ To do this, we should ask if current models are relevant to resource limited settings, if the basic concepts are important and meaningful to the resource limited setting, and if the complexity of adherence captured in the new setting. If the answer is no to any of these, formative research is likely needed to develop an appropriate model or theory for a particular setting.

Both Adamian *et al.* and Ware *et al.* provide extremely helpful insights into understanding adherence and the theory that should go behind any future assessment. Unfortunately no current adherence theory takes into account the complexities of dealing with children, nor do they take into account the social and cultural complexities of resource limited settings. Farther complicating things, not all resource limited settings are equal and may in fact present very different realities for the people who live in one setting versus another. This again supports the need for more qualitative formative research in these settings.

Qualitative Literature Overview:

Several recent reviews of ART adherence literature that focus on studies with qualitative methodology currently exist. Mills *et al.* conducted a review of both quantitative and qualitative studies on adherence to highly active ART (HAART) in both developed and developing countries.²⁹ Their review revealed 37 studies with qualitative methodology. However, only two were performed in developing countries and neither of these looked at children.

Overall, the study found recurring themes within the categories of patient related barriers, beliefs about medication, and daily schedules. A fear of disclosure, forgetfulness, a lack of

understanding of treatment benefits, complicated regimens, and being away from their medications were consistent barriers to adherence across developed and developing nations.

The most common barriers to adherence from the two studies undertaken in resource limited settings (Botswana, Brazil) were issues of access, including financial constraints and a disruption in access to medications. Other barriers which arose in developing countries were co-existing substance addiction, a basic matter of forgetting, financial constraints, complaints of bad taste, side effects, not feeling like the medications were working, trouble incorporating work and family responsibilities with HAART, and difficulties with complex HAART regimens. While themes overlap with those in the high income countries, it is clear that external and structural factors tend to play a larger role in developing countries.

Simoni *et al.* conducted a review of literature on ART adherence, specifically focusing on children.³⁰ They found 50 studies that address this topic in children; however the majority gives only an estimate of adherence rates or quantitative analyses of correlates to adherence. Only two of these studies reported using qualitative methods and neither study took place in a resource limited setting. Regardless, they found that many factors in children are similar to those of adults found in the Mills *et al.* review, namely fear of social stigma related to HIV disclosure, complexity of the regimen, adverse effects, forgetfulness, absence of symptomatology, or the thought of not needing to be on ART because they feel healthy.

However, there are issues specific to children. For instance, some factors are unique to the developmental stage of the child or adolescent. Often youths will focus on gaining rewards and 'living in the moment', hence there is much less concern on planning for the future. Therefore a conscious decision not to take medications is often made.³¹ For the younger children who may not make the decision themselves, caregiver adherence depends on acceptance of the disease and the perceived benefits of treatment for their child. The stronger the disease acceptance and perceived treatment benefits, the more likely they were to adhere to treatment regimens for their children. Data also suggest the ability to cope well with HIV may

be a strong correlate to adherence, which underscores the importance of psychosocial well being in children with HIV.^{31, 32}

No reviews found focused solely on caregivers of HIV positive children. However a number of qualitative studies have been published regarding ART adherence of caregivers, though these studies have been concentrated in developed settings, such as the USA and Europe.^{31, 33, 34} It's clear caregivers play a huge role in maintenance of good adherence for their children. The main factors which appear to influence adherence include the caregiver-child dynamic, the caregiver's attitudes and feelings towards HIV and ART, and knowledge and understanding of the disease and the importance of treatment. It is also clear that the younger the child, the more responsibility the caregiver has in maintaining good adherence.

Overall, there was very little qualitative literature to be found by conducting general literature searches on pediatric ART adherence in resource limited settings. A more systematic approach may be needed to understand what type of literature exists on this topic and if additional studies are needed in this area. Additional literature may be difficult to find however, which justifies the need for a systematic review with a robust search strategy and methods.

II. Systematic Review

Introduction:

To gather a broader understanding of barriers and facilitators of adherence to ART in resource limited settings, I undertook a systematic literature review to assess barriers and facilitators of adherence in the pediatric population. Because prior reviews had been largely unable to draw broad conclusions from quantitative analyses of correlates to non-adherence, the aim of this review was to obtain a better understanding of what types of qualitative literature exist regarding ART adherence in children in resource limited settings, along with their contributions to the literature.

Studies which incorporate qualitative methods have the ability to access information that is often missed in quantitative studies alone. They are able to describe challenges, barriers, and facilitators in ways that cannot be characterized by simple surveys or from statistical analyses on a myriad of dichotomous variables. These types of studies are useful to better understand how patients take ART, what their beliefs and perceptions are about these drugs and their disease, as well as to characterize the lived experiences of those patients on ART.²² Qualitative methods can also be used to confirm the validity of quantitative analyses of barriers to adherence or interventions which address adherence.

At present, there is a 'tremendous paucity of qualitative research in developing settings' that characterizes barriers or facilitators to ART.²⁹ Though prior reviews on qualitative literature have been helpful in shaping our understanding of barriers and facilitators of ART, we are unable to generalize these findings to children in resource limited settings. Since no published reviews to date have specifically focused on this, this review will aim to do so.

The literature on pediatric ART adherence has been largely atheoretical to date.³⁵ This review will also attempt to take findings from papers which meet inclusion criteria and

synthesize them into a broader set of conclusions which may give some additional theoretical background with which to base future qualitative and quantitative research.

Methods:

To understand how qualitative methods have been used in pediatric ART adherence research in resource limited settings and conclusions these studies have drawn, several bibliographic databases were searched. These included PubMed (MEDLINE), EMBASE, the Cochrane Library, and other relevant websites such as those for the WHO, UNAIDS, and the International AIDS Society. Both English and French language articles were included in the search, since many resource limited settings across the world speak French or English as their primary languages. Search dates ranged from January 1st, 1990 through the present (March 15th, 2009), since ART was essentially unheard of in resource limited settings before the mid-nineties. Conference abstracts from international conference the web sites of the International AIDS Society (inception to 2008) and Conferences on Retroviruses and Opportunistic Infections (inception to 2008) were also searched, as well as the National Library of Medicine (NLM) Abstract Database. Other inclusion criteria can be summarized in Table 1.

The following search strategy was used: (pediatric OR paediatric OR infant OR child OR adolescent OR teen OR teenager) AND ((antiretroviral OR anti-retroviral AND agent) OR antiretroviral agent* OR ART OR HAART) AND (compliance OR adherence OR patient compliance OR patient dropout OR barrier OR facilitator) AND (qualitative OR anthropology, cultural OR interviews OR interviews as topic OR chart review OR ethnography OR ethnographic OR narrative OR conversation). The MeSH terms included in this search were: infant, child, adolescent, patient dropouts, compliance, cultural anthropology, and interviews. However the keyword search was more robust than searches utilizing MeSH headings alone. In addition to the electronic search, the bibliographies of relevant articles identified in the search were reviewed by hand and experts in the field were consulted.

For inclusion, articles must have used some form of qualitative methodology for assessment of adherence to ART regimens in non-pregnant, HIV positive children less than 18 years of age or of their caregivers. Types of qualitative research included interviews, focus groups, ethnography, or textual analysis (medical record review, other document review, visual/art representations, or vignettes/conversations). The study settings must also have been a low or middle income country as classified by the World Bank [World Bank website].²⁵ I included studies if they described any individuals less than 18 years of age, even if they included adults as well. Studies that focused on Prevention of Mother to Child Transmission (PMTCT) or post-exposure prophylaxis were excluded. There was no exclusion criteria based on the time frame of the study or number of subjects included.

I analyzed each article to determine study characteristics, study setting, and types of qualitative methodology to determine if they met the inclusion criteria. If the studies met inclusion criteria, they were further analyzed for themes which arose in the qualitative methodology and overall conclusions of studies. Though this process was performed by only one person, ideally this process would include two individuals for reviewing and assessing the articles.

To assess paper quality, I devised a rating scale of good, fair, and poor. Since there are no universally accepted guidelines for assessing qualitative literature, I based these guidelines on several different sources.^{29, 36, 37} The criteria is primarily based on the 'RATS' criteria, which focus on the relevance of the study question, appropriateness of the qualitative method, transparency of procedures, and soundness of the interpretive approach. Quality criteria and the rating scale are summarized in Table 2.

Table 1. Study Inclusion & Exclusion Criteria

Pediatric ART Adherence Papers
incorporating Qualitative Methodology in
Resource Limited Settings

Inclusion:

Dates:	1990-present
Ages:	0-17 Years
Settings:	Low and Middle Countries as defined by the World Bank
Languages:	English, French
Research Designs:	Interviews: Semi-structured Open-ended Focus Groups Ethnography Textual Analysis

Exclusion:

Topics:	PMTCT Post-Exposure Prophylaxis
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Table 2. Quality assessment criteria

Quality Rating	Assessment Criteria
<u>Good:</u> Meets at least 8 Good Criteria:	Good Criteria <ul style="list-style-type: none">• Research question explicitly stated and justified• Qualitative design described• Justification for qualitative design given• Criteria for selecting study sample justified and explained• Details of recruitment procedures and of those who declined to participate described• Methods outlined with details on development given• Examples of methods given• Roles of researchers explicitly stated and potential existing biases discussed• Confidentiality of subjects addressed• Analytic approach discussed in depth, usually with multiple reviewers of the qualitative data• Findings discussed with reference to expositing theoretical and empirical literature
<u>Fair:</u> >3 Good criteria missing; <=2 Red Flags	Red Flags <ul style="list-style-type: none">• Accounts simply analyzed for content, no complex theory generating approach taken• No justification or in-depth description of methods• Findings anecdotal or self-evident in nature• Findings generally full of jargon or trite in nature
<u>Poor:</u> >3 Good criteria missing; >2 Red Flag	<ul style="list-style-type: none">• Researcher has multiple roles, not thoroughly discussed potential biases or maintenance of objectivity• Ethics of study not addressed• Recruitment of consent of study subjects thinly discussed

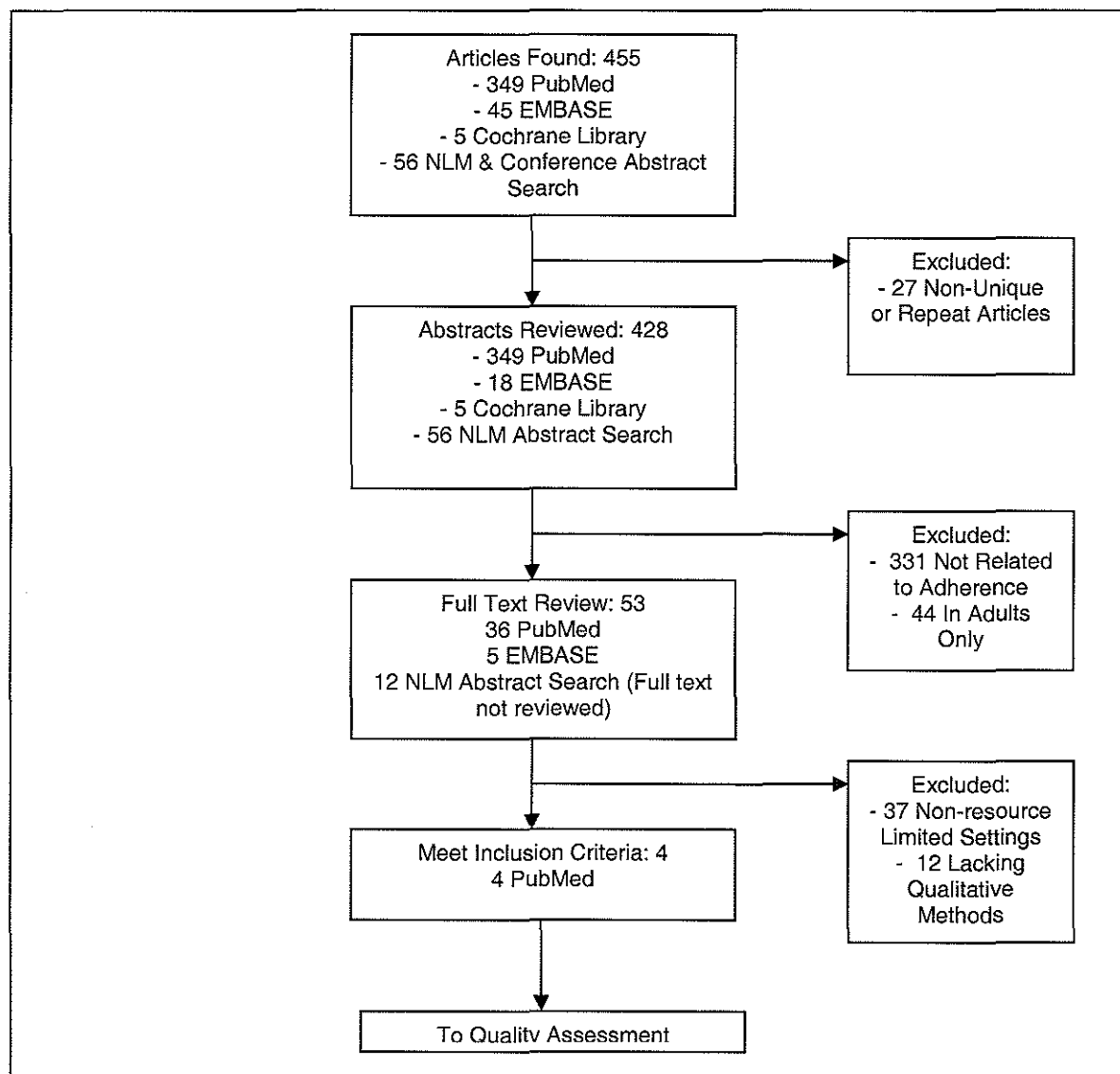
Results:

The systematic literature search identified 445 articles and abstracts. The online search of PubMed yielded 349 articles and the search of EMBASE yielded 45 articles, 18 of which were not found by the PubMed search. The Cochrane Library Database yielded 6 articles, though none of which dealt with resource limited settings. National Library of Medicine and conference abstract databases yielded 56 additional potential sources for review. This strategy resulted in a total of 428 unique articles and abstracts.

All 428 abstracts were reviewed. I immediately excluded articles which did not obviously address ART adherence or were solely focused on adults. This left 53 articles that all

underwent a full text review to confirm the methods used and the location of the studies. If studies did not employ a type of qualitative methods or take place in a resource limited setting, they were excluded. 49 additional studies did not meet criteria, which left 4 studies employing qualitative methods addressing ART adherence in children in a resource limited setting. Each was published between 2005 and 2008, which tends to mark the dramatic increase made in the provision of ART to children in resource limited settings during the last 5 years. The review process is outlined in Figure 2.

Figure 2. Article Selection Flow Chart



For each of these 4 studies, I conducted a quality assessment based on the criteria as outlined in Table 2. Two studies were rated of good quality (Bikaako-Kajura *et al.* and Abadia-Barrero *et al.*) while the two others were of fair or poor quality (Ellis *et al.* and Makoae *et al.*) The studies tended not to provide much, if any, justification for their use of qualitative methods. Also there was generally scant information on recruitment procedures of the subjects or the role of the researchers along with any potential sources of bias from interviewers or data collectors. However, the finding of 'red flags' was all together minimal, with the Bakaako-Kajura *et al.* and Makoae *et al.* studies having two red flags and Ellis *et al.* having three. Because these criteria were a combination of qualitative methods quality assessments collected from other sources, their validity has not been reviewed by experts. Tables 3 and 4 outline the quality criteria each specific study met.

Table 3. Quality Assessment: Good Criteria Met

Study	Question explicitly stated and justified	Qualitative design described	Justification for a qualitative design	Criteria for selecting study sample	Recruitment procedures and declinations described	Methods outlined with development	Example of methods given	Roles of researchers explicitly stated and biases	Confidentiality of subjects addressed	Analytic approach discussed	Findings discussed with reference literature
Bikaako-Kajura, 2006	X	X		X		X	X	X		X	X
Abadia-Barrero, 2005	X	X	X	X	X	X	X			X	X
Ellis, 2006	X	X					X			X	X
Makoae, 2008	X	X		X		X			X	X	X

Table 4. Quality Assessment: Qualitative Study Red Flags

Study	Simple analysis, no complex theory generation	No justification or description of methods	Findings anecdotal or self-evident	Findings generally full of jargon or trite	Researcher has multiple roles, not thoroughly discussed biases	Ethics of study not well addressed	Recruitment of consent of study subjects thinly discussed
Bikaako-Kajura, 2006		X				X	
Abadia-Barrero, 2005						X	
Ellis, 2006		X				X	X
Makoae, 2008			X				X

Of the 4 studies found, only Bikaako-Kajura *et al.* directly assessed ART adherence in children as their primary objective. Adherence was a secondary assessment in the other studies, or rather discussed within the context of a greater topic, such as with stigma or in the overall care of HIV positive children. Still, their findings yield some valuable information about ART adherence in children and allow us to better characterize potential barriers or facilitators. Also, two studies dealt with barriers to adherence from a caregiver's perspective only (Ellis *et al.* and Makoae *et al.*).

*Bikaako-Kajura et al.*⁹ conducted in-depth interviews of 42 HIV-infected children taking ART and/or cotrimoxazole prophylaxis therapy (CPT) ages 5-17, and 42 primary caregivers, at a comprehensive HIV/AIDS clinic in Kampala, Uganda. Overall this study was of good quality, its major fault being absolutely no justification for using qualitative methods, or a discussion of what this type of method would add to our understanding, above and beyond quantitative studies, despite being a purely qualitative study.

They developed an interview guide with semi-structured and open-ended questions that dealt with adherence to ART. They also asked questions regarding actual adherence rates. Though they gave us some information on the nature of their interview questions, few examples are given and we are left to speculate on the specific topics addressed in the interviews.

They found that strong parental-child relationships and disclosure of the HIV status to the child has a strong correlation to good ART and CPT adherence, and that not-disclosing or only partially disclosing made adherence more difficult. The younger the child, the stronger the parental relationship tended to be, which led to less resistance to taking the medications. As the children grew older, those who had not been disclosed to often became suspicious. The study defined this as 'partial-disclosure', where the child is suspicious and asks questions about his or her status, but has not been formally disclosed to. This tended to weaken the child-caregiver relationship and there was much more resistance on the part of the child to take their medicine. Reasons for non-adherence such as side-effects, difficult regimen, or bad taste tended to become much more prevalent in this group. In other words, when the true purpose and benefits of the medications were not known, there appeared to be less motivation on the part of the child to adhere, which then made the job of the caregiver much more difficult. Forgetting was also more common among the non- and partial-disclosures, since the child had less motivation to help the caregiver to remember. ART adherence relies on a strong inter-working relationship between the child and their caregiver.

Irrespective of disclosure status, structural factors such as poverty and stigma were commonly cited as barriers to taking medicine. All other barriers assessed appeared to be secondary to the disclosure status. Children who knew their status were more likely to develop their own strategies to overcome these barriers, such as ways to remember taking their medicine and routines which avoided other people finding out about their status.

*Abadia-Barrero et al*⁸⁸ conducted an ethnographic assessment of 50 orphaned children living in Brazil. The authors measured the life trajectories of HIV positive children ages 1 through 15 years. Data collection relied on standard ethnographic methodologies, which included participant observation and semi-structured, informal interviews. The primary focus was addressing the experience of stigma these children face and how accessing ART has

affected their experiences with stigma. Overall this study was of a good quality rating and met the highest number of criteria, as seen in Tables 3 and 4.

Though the primary focus was not addressing adherence to ART, barriers to taking ART arose within the interviews. The main barrier to adherence appeared in the adolescents, who were almost solely responsible for taking their medications. Because they lived in a group home for orphans, they received much less adult care and supervision at this age than non-orphans. This being the case, often it was a lack of understanding about the regimen that contributed to poor adherence. For instance, children had a poor understanding of the regimen and believed they could take their doses whenever they wanted throughout the day, which meant they were not adhering to the three times daily dosing typical among their regimens. Many of the children, who felt well, would purposefully not take their medications, as they did not understand why they should be taking medicine if they feel well. Often the children would simply forget to take their medicine without any kind of structure, or would prioritize personal enjoyment over taking a dose, such as continuing to play through a game of soccer.

More open communication amongst all the children, and with the few adult caregivers, resulted in less adherence problems. It appears having some sort of support system in place, whether it be peers or adult caregivers, was important to maintaining good adherence levels. By grouping HIV positive children together in homes for orphans, issues with stigma and taking ART appeared to be less of an issue, which may be an important factor in ART adherence of orphaned children.

*Ellis et al.*³⁹ conducted a study to identify factors that predict adherence to drug regimens in Nairobi, Kenya. They recruited 357 adults to participate, however a subset of these were mothers who cared for HIV positive children (N=233). Both quantitative and qualitative methods were employed. Two quantitative surveys were developed to identify factors that predict adherence of drug regimens, while the second was developed solely for the subset of mothers regarding adherence in giving medicine to their children. They used focus groups as

their qualitative method, which were developed to farther probe answers from the quantitative surveys.

Though this study had a 'poor' quality rating based on the qualitative study assessment scale, likely this is due to the fact the paper focused more on the quantitative methods and did not devote much of their text to describing their qualitative methods. None the less, we know little about study sample selected to undergo the focus groups, how and why participants were selected, how bias may have been addressed in a setting where information is shared with a group, or anything about the specific questions asked of these focus groups. Also, only some of the children were on HIV drug regimens. The study focused on drug regimens in general, so not all the findings may have been specific to ART. They do not distinguish which findings are specific to which type of drug regimen.

The focus groups revealed that among the mothers who provided medication to their children, they found that lack of food, financial constraints, and timing of difficult regimens compromise the ability of mothers to adhere to their child's medication regimen. The mothers also report often simply forgetting to give the medication all together or having extreme difficulty in getting their child to take medication. The latter often occurs because of the large size and bitter taste of the pills. Further, when the child is resistant to take their medicine, the mother tends to report being unable to get the child to adhere as well over the long term.

Most mothers agreed that their child's health is paramount to them and would rather supply the child with medicine than themselves, however they only travel to the doctor when absolutely necessary and often are delayed in seeking care. This hesitation may be due to the structural barriers which make it so difficult to travel to the clinics to receive refills and in some cases pay for their medications. These women tended to agree that they had faith in western medicine and that hesitation in seeking care or refills was not due in part by belief the pills were not helping.

Lastly, *Makoae et al.*⁴⁰ analyzed the challenges which caregivers encounter while providing care to HIV positive family members at home in Lesotho. Adherence to medication was addressed as part of their general care. The study enrolled 21 family caregivers to undergo in-depth qualitative interviews. Not all caregivers were in the care of children, some were also caring for adults. The study does not provide characteristics of the study sample or to whom each caregiver provided their care. Therefore we do not know how many caregivers were caring for children or the children's characteristics, but we are told in the findings that there is at least one mother, one father, and one grandmother who were caring for children during the study.

Findings are mostly reported as example quotations which highlight certain barriers to HIV care. Since the number of adults caring for children is quite small in this study and no rigorous exploration of themes or qualitative analysis within this sub-group, the findings are mostly anecdotal with relation to medication adherence. Also, recruitment procedures are thinly discussed. Therefore this study received a 'fair' quality rating.

The findings as they relate to ART adherence and children are minimal, though they produce a few findings. Barriers discussed mainly deal with cost and availability of medicine as an issue. These are not unique findings to this study. However, a more original topic discussed is that of the caregiver's health status and how disruptions in their health tend to negatively affect the care of their children. For instance, if a caregiver is ill such as with an acute illness, their ability to ensure adequate care, including receiving all medications, is compromised. In these cases, the child must be relied upon to some extent to take their own medication. Relying on other family members who may not know the proper medication regimens or even know the HIV status of the child can lead to poor adherence.

These four studies were all significantly different in scope, study design, and study population and it is difficult to produce a set of pooled results from all four studies. The characteristics and findings of these studies are summarized in Table 5.

Table 5. Study Setting & Design, Overall Quality Rating, and Summary of Results

Study	Study Setting & Design	Overall Quality Rating	Barriers to ART Adherence	Facilitators to ART Adherence
Bikaako-Kajura, 2006 ⁹	Kampala, Uganda Qualitative interviews with 42 children and caregivers	Good	<ul style="list-style-type: none"> ○ Non-Disclosure of HIV status to the child ○ Financial constraints/poverty ○ Stigma with HIV and taking medications ○ Other barriers secondary to disclosure status 	<ul style="list-style-type: none"> ○ Strong parental-child relationship ○ Good communication between child and parent ○ Disclosure of HIV status to Child
Abadia-Barrero, 2005 ³⁶	São Paulo, Brazil Ethnographic study of 50 orphaned children	Good	<ul style="list-style-type: none"> ○ Lack of adults to supervise and assist with the medicine ○ Poor understanding of regimen ○ Feeling healthy ○ Poor communication with adult supervisors 	<ul style="list-style-type: none"> ○ Living in an environment with other HIV positive children ○ Support from other children or adults
Ellis, 2006 ³⁹	Nairobi, Kenya Focus groups of mothers who care for HIV positive children	Poor	<ul style="list-style-type: none"> ○ Financial constraints/poverty ○ Lack of food ○ Resistance from children due to difficulty of regimens or poor taste ○ Difficulty with transportation 	No facilitators reported
Makoae, 2008 ⁴⁰	Lesotho Qualitative interviews of caregivers with HIV positive children	Fair	<ul style="list-style-type: none"> ○ Financial constraints/poverty ○ Difficulty with transportation; availability of medicine ○ Poor health status of caregiver 	No facilitators reported

Discussion:

This systematic review presents the first comprehensive review of the qualitative methodology used to better understand pediatric ART adherence in resource limited settings. It is immediately evident that there is a paucity of this type of research, which supports this assertion noted in a number of other articles.^{16, 29} Because these studies use heterogeneous methods and study populations, it is difficult to draw broad conclusions or to generalize findings based on all four studies. However when looking at the results as a whole, common themes that arose within these studies were those of structural barriers (financial constraints and

transportation) as well as situations where the caregiver is impaired, or not present, for motivating or assisting the child to properly take their medications. Also, conflict between the caregiver and child appears to serve as a barrier to good adherence.

The quality and breadth of information obtained from the Bikaako-Kajura *et al.* study⁹ was much more in depth than the other three studies and was most valuable to the understanding of this topic in resource limited settings. Their primary objective was assessing pediatric ART adherence, whereas the other three studies only address ART adherence within the context of larger objectives such as dealing with stigma, medication adherence relating to all medications, or with overall care of HIV positive individuals. Therefore the results from the other three studies do not have as much significance to this review and typically their findings were more anecdotal since there were fewer subjects speaking on ART adherence with which to draw conclusions.

Significant, and well explored, in the Bikaako-Kajura *et al.* study was the issue of non-disclosure and its effects on adherence. The underlying theme was conflict created between the child and parent due to this issue. Many of the children in this study were suspicious of their HIV status and were considered 'partially disclosed', meaning they may have had some idea about their status, but no one had confirmed it specifically. This created an atmosphere of tension and lack of trust between the child, caregiver, and clinical staff, especially for older children or those nearing adolescence. Without a strong rationale behind taking such medications, there is little motivation on behalf of the child to do so. The findings in the Abadia-Barrero *et al.* study seem to support Bikaako-Kajura *et al.*, where they note poor communication with the child and lack of a strong caregiver-child relationship seemed to create conflict, lack of motivation, and adversely impact ART adherence.

Judging from these studies, it is clear maintaining good adherence was difficult for many children and some sort of adherence strategy is needed. This strategy may need to be unique to each child, however employing both the child and a caregiver into a given strategy is the most effective means of doing so. Without a partnership, adherence entirely depends on the

caregiver support strategy, availability, and willingness to give medicine as prescribed, which is much more difficult as a long term strategy. The common facilitator noted between Bikaako-Kajura *et al.* and Abadia-Barrero *et al.* studies was that of providing a support system to the child. This could be having other HIV positive children to rely on for support, or having an adult caregiver with whom there is a relationship of trust.

Three of the four studies noted structural barriers as significant barriers to good adherence. This is not surprising, as previous reviews looking at children in some developed settings and adult populations in resource limited settings have also found that structural barriers such as financial constraints, access to medications, and transportation are significantly associated with maintaining good adherence.^{16,29} The difficult question is how to address and overcome these structural barriers in resource limited settings, which can be extreme for both children and adults.

This systematic review suggests that the need for strategies to overcome child-caregiver relationship and structural barriers is paramount. Training social workers or support staff at clinics which provide ART may be effective in helping children and caregivers to develop coping strategies for structural barriers. This could employ techniques such as Motivational Interviewing, which have been used to promote adherence in developed settings.²⁷ Formation of child peer support groups for behavioral reinforcements may also be useful. This strategy may only be available to children who know their HIV status, however peer support groups for adult caregivers of children who do not know their status may be a useful alternative.

For children who do not know their status, Bikaako-Kajura *et al.*⁹ recommend counseling to discuss the nature of the caregiver-child relationship, relational barriers, and ways this can be improved, without necessarily having to address their ART regimen or HIV itself. A better overall relationship may translate into better communication regarding their medication regimens. Children who ask many questions about their drug regimen or with suspicions about their status may need special attention. There may be specific psycho-social issues regarding

this sub-set of children and specific mechanisms of support should be available at the ART clinics for both the caregiver and child.

Ultimately, caregivers should be encouraged to disclose the HIV status to the child. This is also not easy for those living in settings where the stigma associated with the disease is great and other family members may also be unaware of the child's status. However, despite these problems, previous studies show that children generally want to know their status and it appears this could facilitate better ART adherence.²¹

This review has a number of important strengths. The methods employed to tabulate these findings come from a multi-step process which is clearly outlined in Figure 2. A number of different search strategies were employed with the aid of librarians who were very familiar with the databases and trained to determine which strategy would carry the best balance of sensitivity, yet still keeping a narrow enough focus of the topic.

Pooling the results seemed infeasible due to the heterogeneity of methods. Because there were few studies, this seemed largely unnecessary as well, with only four studies meeting inclusion criteria. While a number of themes arose among the studies, they can be easily surmised in Table 5. Though the quality criterion has not been validated, it is taken from a number of sources which assess the quality of qualitative research. Since I found a range of good, fair, and poor quality studies, it is reasonable to believe this criterion is capable in discerning between well done studies and those whose methods are lacking.

I do acknowledge the number of studies found with this method is quite small. Whether a more robust search strategy exists or a more in-depth search of additional databases or abstract searches would have yielded more studies is unknown. However I believe this is unlikely, as systematic reviews which have looked at this topic in developing settings have found the same paucity of qualitative studies. One previous review from 2006 found only 37 studies ever using qualitative methodology, in any setting, dealing with both adults and children and assessing ART adherence.²⁹ Narrowing down to children only, there were a mere 8

studies conducted in developed settings. Indeed, the fact that even four studies were found in resource limited settings that dealt with this topic is somewhat surprising.

Other limitations to this review should be acknowledged. Because this review has only one author, there was no way to validate the review process or selection of studies to assess for agreement. Only studies in English and French were considered, though no studies in French were found. It is still possible some relevant studies in other languages may have been overlooked. Publication bias could potentially be a concern. However since qualitative studies typically represent formative research, I believe it is unlikely that some qualitative findings would selectively remain unpublished. Further, two of the four studies did not have ideal methodological strength and their findings may not have great significance for this reason. It may also be incorrect to assume findings from one resource limited country to another will be applicable. There is great breadth between populations in these countries. The children of Brazil may face a very different reality from those of Uganda or Lesotho when taking their HIV medicines.

More high quality studies are needed from different resource limited settings to better understand the barriers and facilitators of ART adherence in children. Development of an improved theory and best practice guidelines for pediatric ART adherence are severely needed. Also, more quantitative studies that employ culturally appropriate models to accurately measure adherence and a better established definition of what 'good adherence' means with regards to children in resource limited settings are warranted.

Future qualitative research in this area will have a number of questions to answer. It will be important to determine if indeed the disclosure status of the child plays a strong role in maintaining good adherence in other settings, aside from the Bikaako-Kajura *et al.* study. The perspective of the caregiver will especially be important to assess, since the adherence of the medications depends heavily on them. How do these caregivers approach maintenance of

good adherence in non-disclosed children? How are strategies different, and perhaps more successful, with caregivers of disclosed children?

Though we know that structural, cultural, and social barriers can make ART adherence difficult in children, understanding the 'why' behind these barriers will be helpful to developing strategies to overcome them. Along these lines, we also need more information on facilitators to good ART adherence and a better understanding on why certain practices or strategies tend to aid in adherence. The studies in this review did not focus on identifying and exploring facilitators, though facilitators were briefly mentioned in two of the studies.

As found in prior reviews, qualitative studies are superior at identifying and understanding patient-important barriers and facilitators and should set the basis for future quantitative works.²⁹ More studies will be useful to support and add to the findings of these four studies, and to determine whether barriers and facilitators in one resource limited setting are similar to others. Though three of the four studies found in this review were performed in Sub-Saharan Africa, more are needed in this region, where 90% of pediatric HIV cases exist and scale-up of ART access to children continues.

None of the studies provided information about the length of time children had been prescribed ART, so it is difficult to make comparisons between the children with-in, or between, studies. It is also likely adherence practices change over time, especially when illness improves or side-effects increase. Future studies may make better measure of the time frame of the ART regimens they are assessing and correlate this as a barrier or facilitator to good adherence.

This review identified a range of barriers and facilitators of adherence for children taking ART in resource limited settings. Though certainly not comprehensive, this information can serve as a guide for future interventional research to improve adherence rates. Clinicians or support staff practicing in resource limited settings can use this information to engage in open discussion with patients, promote adherence, and even identify barriers and facilitators in their own population.

ART adherence is crucial to maintaining the health of HIV positive populations. Though good adherence may become easier over time with simplified regimens and increased cultural acceptance and understanding of HIV, maintaining good adherence and measuring this adherence in resource limited settings will continue to provide challenges. Additional research geared towards children will shed light on best clinical practices and bring the focused attention necessary on this area required to address it.

III. Research Plan

1. Overview and Rationale

Background:

The Democratic Republic of the Congo (DRC) is a war torn nation of around 63 million inhabitants.⁴¹ Since 1998, on-going conflict in the eastern part of the country has been characterized by extreme violence, mass population displacements, widespread rape, and a collapse of public health services.⁴² This has been dubbed 'Africa's first World War' due to the number of nations involved and population affected. To date, nearly 4 million people have been killed as a result of the unrest, the highest number in any conflict since World War II.⁴² In recent years, the violence has ebbed somewhat due to the signing of peace accords by various factions and the presence of UN peacekeeping troops. However outbreaks of violence in the eastern part of the country are still common.

The DRC (formerly Zaire) was one of the first countries to develop and HIV/AIDS prevention program in the 1980's. Due to the political, social and economic impacts of conflict during the 1990's, this region unfortunately now lags behind many other African nations in the development of a stable public health infrastructure. This means that continued progress in HIV prevention and treatment, among many diseases, has been slow. The capital city of Kinshasa in the western part of the country has fortunately received relative stability in recent years and some progress has been made in terms of addressing the HIV epidemic.

In November of 2004 the Sustainable Antiretroviral Access (SARA) Program was initiated at several of the public hospitals in Kinshasa. This program is a collaboration between the University of North Carolina – Chapel Hill and the Kinshasa School of Public Health. Their goal was to provide antiretroviral therapy to both HIV positive children and adults within the Kinshasa region and to assess the feasibility of such an undertaking.

Despite the fact that one of the earliest known strains of HIV was detected in the Kinshasa region dating from 1959,⁴³ the DRC has remained on the low end of HIV prevalence rates, relative to sub-Saharan Africa. Data from 2007 estimates the HIV prevalence range on the order of 400,000 to 500,000 cases.⁴¹ 37,000 to 52,000 of these cases are estimated to be in children less than 15 years of age. These numbers put the countrywide prevalence at a rate of around 1.2-1.5%. However, sentinel site surveillance in pregnant women suggests that the prevalence is higher in urban settings. A 2004 survey revealed HIV prevalence to be around 4% in Kinshasa and as high as 7-9% in other urban settings.^{41, 44} The accuracy of this HIV prevalence data is difficult to ascertain. In a war torn region such as the DRC, it is possible these numbers are under reported since accurate data measurement is difficult in many areas of the country. Other estimates of HIV prevalence put the total number of people living with HIV upwards of 3 million.⁴⁴

It is clear that provision of ART has also lagged behind in the DRC and is limited in many provinces. Though the prevalence may be low relative to other sub-Saharan African countries, those with HIV typically do not receive adequate care. The country is large, has a sizeable mobile population, and health care services are inadequately decentralized. There is a severe shortage of human resources trained to deliver antiretroviral therapy.⁴⁴ Of those HIV positive individuals in need, only 20% to 29% were estimated to be receiving ART, most of whom live in Kinshasa.⁴¹ Only 1,632 HIV positive children are recorded as receiving ART, which is a mere 3.1% to 4.4% of all HIV positive children in the country.¹

The SARA Program has begun to address the need for HIV treatment in Kinshasa, especially with regards to children. As of September 2008, the SARA program served 737 HIV positive children <18 years of age, 503 of which were started on ART. The recommended first-line drug regimens are stavudine + lamivudine + nevirapine or stavudine + lamivudine + efavirenz.⁴⁴ The average cost of first-line treatment is about \$348 (USD) per person per year.

Overall, more study is needed on nearly all aspects of HIV prevention and treatment in the DRC. Years of civil unrest have damaged the health care delivery system and the ability to successfully perform research in many areas of the country is compromised.⁴⁴ Much of the research done in other areas of sub-Saharan Africa may be generalizable to the DRC, but not all. This is especially true with subjects that may address culturally specific behavioral or social issues, such as adherence to ART.

ART Adherence in Kinshasa:

Access to ART has lagged behind for children all across sub-Saharan Africa. As mentioned, the DRC appears to be no exception. Data on adherence to ART in the DRC is not surprisingly sparse, considering the relatively small number of children currently taking ART regimens.

Some preliminary data on adherence does exist from children receiving care at the Kalembe Lembe Pediatric Hospital (KLL) in Kinshasa, collected through the SARA program. The data comes from provider administered questionnaires to both caregivers accompanying children at clinic visits and from children themselves, who are over 12 years of age.

This data reveals >99% of caregivers and children >12 years of age are reporting 100% adherence within the last 2 days along with zero days of missed treatment within the last month.⁴⁵ This is well above expected norms of children in similar settings, where favorable adherence rates range from 50% to 80%.¹⁶ These data also lack the expected variability in adherence rates between subjects and the figures are likely inaccurate. Failure rates of ART have not been well recorded in children at the KLL Pediatric Hospital. However, failure rates of first line ART regimens in children are increasing in number and have been shown to be twice as high as adults in similar settings.⁴⁶

It is known that provider administered questionnaires are vulnerable to a social desirability bias and can lead to inflated figures on ART adherence. As mentioned in Section I, this method is

not optimal for measuring adherence and the SARA adherence rate data is likely over inflated, however it is difficult to estimate the degree of this.

Study Rationale

Pediatric adherence to ART has not been widely assessed in sub-Saharan Africa, where over 90% of children living with HIV are located.⁹ Because the number of children accessing ART is rising substantially each year, best practice guidelines to ensure high rates of adherence is needed. Without an in-depth understanding of what makes these regimens more difficult, or perhaps easier, in sub-Saharan Africa and other resource limited settings, these best practice guidelines will be difficult to synthesize.

Since little data exists on adherence to pediatric ART regimens in Kinshasa and in resource limited settings in general, the Kalembe Lembe Pediatric Hospital represents a prime target for farther study. I am proposing a study which assesses barriers and facilitators of adherence to ART regimens in children through qualitative, formative research.

Qualitative methods represent a practical place to begin study in this setting. This type of methodology can be used to inform the development of more valid, culturally appropriate adherence measures and a contextual adherence theory and can serve as validation to any future quantitative studies addressing adherence in Kinshasa.¹⁶ As described in Section II, very few qualitative studies assessing pediatric ART adherence in resource limited settings exist, and even fewer are generalizable to the context of Kinshasa.

2. Research Plan Procedures & Methods

Setting:

The SARA program is a longitudinal, prospective cohort of comprehensive HIV care and management, including ARV treatment, for adults and children in Kinshasa, DRC. The program operates at several public hospitals and clinics in Kinshasa. All enrolled subjects receive primary HIV care, including management of opportunistic infections and psychosocial support.

Subjects who meet specific criteria are also started on ARV treatment. For children, this includes being HIV positive, aged 0 through 17 years, who had been receiving HIV/AIDS care before the start of the program or who were identified HIV positive through the expanded HIV testing strategy (op-out system) at the KLL Infectious Disease Unit. Children under 18 months with confirmed HIV infection with a positive viral test result are also eligible to participate in the SARA program. All participants in this study will be recruited from the subset of children receiving ART within the SARA Program at the KLL Pediatric Hospital in Kinshasa.

Subjects, Recruitment, & Consent:

During a six week period over May and June 2009, we will recruit approximately 40 study participants for qualitative in-depth interviews. These participants will be children 8 years of age or older who are actively receiving regimens of ART, enrolled in the SARA program, and receiving care from KLL physicians and staff. We will also recruit the adult who accompanies the children to their regularly scheduled clinic visits. If more than one adult accompanies the child, we will recruit the one who has the most active role in caring for the child. We will also recruit caregivers with young children below the age of 8 to participate. Specific inclusion and exclusion criteria are outlined in Table 6.

Participants will be selected from the daily SARA appointment list at the KLL HIV clinic. The psycho-social support staff at KLL, typically trained social workers, will approach caregivers which meet inclusion criteria after they have completed their daily clinic visit. They will be asked to remain in their clinic room by the clinic staff so they can be approached in a private manner. The qualitative interviewer, who is fluent in Lingala and French, will approach the caregiver and tell them we are interested in asking some questions about themselves and their child for a study that UNC-Kinshasa School of Public Health and the clinic are performing. We will not mention anything about medications, HIV, other illnesses, or of the exact nature of the interview questions at that time. We will explain that we would like to sit down and interview them in a separate private room by themselves, overview the time it will take, and that there will be compensation for completing interviews.

If they agree, we will take the caregiver to the private, closed off room in the clinic where the consent forms will be provided and the study objectives described in greater detail, as per the script in the attached Interview script and questions. If they refuse to participate, reasoning will be documented if given. During the interview, the child (and other accompanying children) will remain in the care of the clinic staff or other research personnel. The caregiver will be informed that they may opt out at any point during the process without penalty and compensation will still be provided for their time given.

If consent is given for children over the age of 8 to participate in the study, the qualitative interviewers will interview them in the same private room alone, after completion of the caregiver interview. Their caregiver will be asked to remain in the clinic waiting area.

For recruitment purposes, a history of non-adherence will be elicited in two ways. First, selection will come from previous medical records, which the clinic staff will review prior to the clinic visit for documentation or suspicion of non-adherence to ART. Since we will be working in close collaboration with the clinic staff, we will also elicit non-adherence from clinical suspicion during or immediately following the scheduled appointment. The physicians, nurses and psychosocial support workers will be instructed to alert study personnel if this is the case.

If selected from medical records, the definition of non-adherence will be documented based on the written record. If selected based on clinical suspicion, the physicians and/or psycho-social support workers will be asked to explain their reasoning (i.e. admitted non-adherence, unusual failure of first line therapy, falling viral load or CD4 count, continued poor clinical presentation)

We will attempt select 1 to 2 patients (a child and their caregiver) per day for interviews over a 2 month period, beginning in May of 2009 and running through July 2009. We will attempt to recruit an equal number of male and females, different ages, disclosed and non-disclosed, as well as some caregivers who care for children below 8 years of age. However, we may be limited by selecting for patients with a history of non-adherence. Because final examinations are occurring for school

children during this time, we may also invite adult caregivers and their child to return on Saturdays for the interviews.

Typically, qualitative interviewing is an iterative process. It continues until a set of themes on particular topics begin to arise and reach saturation. Previous studies on ART adherence have reached saturation of themes with anywhere from 20 to 50 participants.^{9, 32, 40, 47} Therefore we will conduct as many interviews as feasible within this time frame, which we anticipate will be anywhere from 30 to 50 adult caregivers and children.

Table 6: Inclusion & Exclusion Criteria

Participant	Criteria
Children	<p>Inclusion:</p> <ul style="list-style-type: none"> (1) Aged 8 to 17 years and enrolled in the SARA program (2) Actively receiving care at KLL for at least 6 months (3) Have been prescribed and actively taking an ART regimen for at least 6 months (4) Have a documented history of poor adherence noted within their medical record or a clinical suspicion of non-adherence supported by the physicians, nurses, or psychosocial support staff at KLL at the time of the clinic visit. (5) Must speak French or Lingala (6) Willingness to be interviewed alone
Adults	<p>Inclusion:</p> <ul style="list-style-type: none"> (1) At least 18 years of age or older (2) Accompanying a child aged 6 months to 17 years to their scheduled clinic visit (3) Must have known the child for a minimum of 6 months (if not a primary relative) (4) Must speak French or Lingala (5) Willingness to be interviewed alone (6) The child they accompany must have a documented history of poor adherence noted within their medical record, or a clinical suspicion of non-adherence supported by the physicians, nurses, or psychosocial support staff at KLL at the time of the clinic visit. (7) The adult care giver is aware of the child' HIV status old
Children & Adults	<p>Exclusion:</p> <ul style="list-style-type: none"> (1) Adult and child (if 8 years of age or older) are unwilling to be separated for interviews (2) Both adult and child do not speak either French or Lingala (3) The participant is personally known to the qualitative interviewer or other study personnel

Qualitative Interviews:

The interviews will assess the opinions and experiences of the study participants in dealing with ART regimens. General themes explored with adult caregivers will include overall attitudes towards ART regimens, perceived benefits or liabilities of ART, health beliefs on ART and on HIV, what good adherence means to them, perceived barriers in carrying out regimens as prescribed, facilitators which aid ART adherence, and an assessment of the child's specific adherence rate. With the children, we will explore similar themes. These include beliefs regarding ART and HIV as well as what they perceive to be barriers and facilitators to good adherence. Throughout the process, we will explore specific instances of missed doses.

Trained qualitative interviewers who are fluent in French and Lingala, the local language, will carry out all recruitment procedures and conduct interviews, under the supervision of the study coordinator and clinic staff. These interviewers will follow scripts that have a list of themes and corresponding questions with probes to be addressed with the study participants. The interview script can be seen in Addendum I. Questions were based on prior literature searches which explored potential barriers to ART adherence. The semi-structured nature of the interviews and multiple question probes will allow the interviewers to explore topics in detail which are relevant to each participant. This flexibility will allow us to explore and clarify emerging issues pertinent to ART adherence as they arise.

There will be a day of orientation to the study for the qualitative interviewers and clinic staff, before recruitment begins, explaining the study protocol for adults, children who have had HIV status disclosure, and children who are HIV status naïve. There will be several practice runs through the study protocol with study personnel, the clinic staff, and the qualitative interviewers that will serve as pre-testing. The study team will comb through, in-depth, the recruitment procedure, the consent process, and each of the three interview types (adults, status disclosed child, and non-disclosed child) for potential problems and areas for improvement.

The qualitative interviewers will have received previous training on qualitative interview techniques and research methods. Recruitment procedures are further outlined in the Standard Operating Procedures in Addendum II. Interviews will be carried as per the interview script and question forms, attached submitted as the Interview Script Form. The interview script and questions will be translated into French and Lingala with the aid of translators and input from the clinic staff.

Participants will be taken to a private, closed off room within the hospital for the consent process and the interviews. The initial interview script will serve to introduce the study and to de-stigmatize the issue of non-adherence. Some information on the caregiver and their relationship with the child will be ascertained from an initial questionnaire administered after the initial script but before the qualitative interview questions begin. Interviews will last anywhere between 30 to 120 minutes for the caregivers and 30 to 90 minutes for the children and they will be recorded by a digital sound recorder.

Keeping interest and engagement of some of the younger children will be challenging, so interviews will end early if the child no longer remains focused and can no longer be engaged despite several attempts. Caregivers and children will be interviewed separately. Children will be supervised by research assistants while the caregiver interview takes place. If the child is younger than 5 years of age, he or she may stay with the caregiver during the interview, if the caregiver wishes, though we will encourage solo interviews. If the caregiver and child (5 years or older) do not wish to be separated, we will not conduct the interview, as the presence of one another may bias the responses.

For children who have not been informed of their HIV status and do not know the true nature of their medications, we will use a separate interview script. It will be important to address the difficulties these children face with their regimens without alluding to the true nature of their medications or that they may have any specific type of disease or condition.

Interviews will be transcribed from the interview audio files and entered into Microsoft Word (Redmond, WA). During this process, they will be translated into English directly from Lingala. Also, demographic information, data from Section I of the interview script and questions 'zero' from both child interviews will be entered in to a Microsoft Excel database for storage. These files will be brought back to the US for analysis. Used interview script forms and consent forms will remain in Kinshasa for record keeping purposes and storage.

Benefits and Risks to Participants and Safety Measures:

There may be no immediate direct benefit to the individual study participants, other than an increased awareness of the specific challenges each caregiver and child faces in administering ART regimens. However, increased introspection and identification of barriers may potentially serve to reduce and overcome such barriers.

The findings of this study will serve to aid the SARA Program staff at KLL, and others who provide pediatric HIV treatment in resource limited settings, to better understand why caregivers have trouble administering ART to their children and why children may not always take all of their medications.

Virtually all research studies carry inherent risks to personal privacy, and this study will be no exception. This includes the possibility that personal or private medical information may be inadvertently divulged to non-research personnel. Specifically, divulgence of the HIV status of the caregiver or child may cause difficulties within the participants' community if inadvertently disclosed to other people in their community. This may cause emotional distress, embarrassment, and a feeling of mistrust towards the clinic and towards participation medical research.

Qualitative interviewers and staff may have access to identifying information. However, they have had training in research methods and in keeping the confidentiality of research subjects. They adhere to the research practice standard set forth by UNC and the SARA Program.

We will take every precaution to ensure that identities of the study participants remain blinded to all study personnel and that recruitment procedures do not divulge any information regarding the study until located in a private location. At the beginning of the interview, post-consent, each participant will be assigned a study identification number by the PI (ie. A(Adult)#007 or C(Child)#007). All study forms and audio tapes will identify participants only by this assigned study ID number. Participant names will not appear on any forms or the audio tapes. Their identities will be linked with their ID numbers in a separate MS Excel file. This will be a password protected file and will be stored with study personnel in Kinshasa. This file will be destroyed after completion of the study analysis.

Disclosure of HIV status to naive children is a serious concern. Children who have not been disclosed of their HIV status, or have only partially been disclosed, have been shown to have worse adherence rates when compared to children who have been disclosed of their status.⁹ Therefore, information collected from these children will be extremely valuable to the study, as they may share a very different perspective on taking their medications than children who know their HIV status. Every precaution will be taken to assent and interview these subjects in a manner in which does not divulge the nature of their medications or their relation to any specific condition or disease.

The interview script for non-disclosed children does not refer to HIV, the purpose of their medications, or that their medicine may be for a specific cause at all. However, we cannot ensure that interviewing these children will not raise their suspicion or result in an increased interest in the true nature of their medication regimens. There is potential for psychosocial harm to the child if their status is inadvertently divulged or discovered before their caregiver has deemed them ready, as well as caregiver anger and a feeling of misplaced trust in our research practices. The caregiver will be informed of these risks prior to consent and be allowed to view the questions that will be asked of their child.

Consent forms will be provided to adults for their participation and adults for their child's participation. These will outline the purposes of the study and pertinent risks and benefits for participation. The U.S. Department of Health and Human Services suggests assent should be sought from children aged 13 and older (Department of Health and Human Services (DHHS), 2001) so assent will be obtained from adolescents aged 13 – 17 years of age. The forms will require a signature. If the participants cannot read or wish not to read it themselves, the interviewer will read the forms out loud and can sign with a stamped fingerprint.

Compensation to Participants

Sub-study participants will be compensated for their time at a rate comparable for payment of citizens' time in Kinshasa, Democratic Republic of the Congo. Caregivers will be compensated \$5 (or equivalent Congolese Franc amount) for completion of a full interview and an additional \$5 for their child's time, if they are eligible and participate in the study. Compensation will occur at the end of the interviews in the confines of the private room. Snacks and beverages will also be provided to both adult and child participants at the beginning of the interviews and throughout, as per interview script.

Analysis of Data

Qualitative data will be entered into software that aids in qualitative data analysis and analyzed. With the aid of these programs, codes will be assigned to conceptual patterns or themes which arise in the interviews. At least two study personnel will work through this process until a consensus of these patterns or themes are reached. We will draw conclusions on barriers and facilitators to ART adherence based on these patterns or themes and the characteristics of the adults and children to whom they apply.

We will also collect some demographic data on each study participant. This data will come from the first section of the interview script and will be used to quantitatively describe the characteristics of the study population. Analysis of data will occur during the months following completion of the interviews.

IRB Application

Approval for study was acquired from the University of North Carolina internal Review Board (IRB) on April 27th, 2009 and from the Kinshasa Ethics Review Committee on June 5th, 2009. The Standard Operating Procedure, detailing the study protocol as outlined in the IRB application, can be seen in Addendum II. This study will ultimately be reviewed for possible publication once the analysis is complete.

IV. Implementation of Research Plan and Lessons Learned

Feasibility of the Research Plan

Throughout the course of six weeks in Kinshasa, Democratic Republic of the Congo, I was able to implement the research plan and gauge the feasibility of performing this study, and qualitative research in general, in a resource limited setting. Overall I found that with the correct resources and preparation, a study implementing qualitative interviews or other qualitative methodology is quite feasible and can yield meaningful results.

The key aspect to performing qualitative research is a significant understanding of the society and culture of those subjects who are solicited for participation in such studies. Because these types of studies involve direct interaction with locals, it is imperative that the protocol take into account cultural norms. For instance, when dealing with a subject such as ART adherence, it was extremely important to know that Congolese people are typically polite in such a way they will almost always tell you what they think you want to hear. Therefore we had to make extra care in explaining to the research participants that we wanted their true opinion, not simply what they thought was the 'right' thing to say.

It was important that the majority of the study team were local Congolese. This was especially true of the interviewers and participant recruiters. It would be impossible for foreigners to travel to this setting and perform these interviews themselves, and without bias, since they would inevitably lack an understanding of the mannerisms of a culture that come from being raised and living within it. Having the study team look over the methods of the study, namely the interview questions themselves, was also important to ensure these questions were culturally relevant and would make sense to participants. For instance, one question asked about their thoughts on how society's attitudes made it difficult to adhere to their medicines. However, 'society' could be construed in many different ways to a Congolese and we needed to be much more specific and provide examples about what the question meant. Further, when

asking about facilitators, questions regarding the improvement of motivation were to be asked, however there was no direct translation of the word 'motivation' into Lingala and the question needed to be reworded to accurately obtain the desired information.

It's also important to respect and understand the different cultural values associated with medical care and certain diseases, such as HIV. It can be challenging for patients to open up about HIV, even to the medical staff to whom they are familiar with. Throughout sub-Saharan Africa, this topic has typically been regarded as taboo and can be a form of 'social suicide' in some situations to admit yourself or a family member as HIV positive. It was extremely important to make clear to the participants that the interviewers were an extension of the medical staff at KLL hospital, and that the same strict standards of confidentiality applied to them, and to all of the study staff, as well. Without this understanding, we likely would not have received open and honest answers about their HIV medication regimens.

Probably the most challenging barrier of the study was addressing the safety of children who were not disclosed of their HIV status. This turned out to be a major barrier in caregivers allowing their children to participate. Therefore we had to make extra clear and give extra effort in allowing the caregivers to understand exactly what would happen during their child's interview and that our study team was very cognizant of this issue. Simply glazing over the issue with the caregiver and covering it quickly was not sufficient. We needed to pause at this issue and make sure the caregivers were comfortable and had time to receive assurance and have questions answered. Otherwise we risked a reflex refusal from the caregivers to let their child to participate when prompted, as if it were too complicated or risky to even consider. Throughout our first day of interviews, we had time to adjust to this and improve our ability of communicating on this issue.

Local staff had to be hired to carry out the study. The only disadvantage to this in the realm of qualitative methods is the hiring of a staff that is well trained in this type methodology. Whether this is interviews or focus groups, it takes some significant training and experience to

properly carry them out. With the aid of the UNC-DRC staff and my own personal preparation, I was able to conduct training of these interviewers. Fortunately our staff had already been trained before. However, we developed a refresher session on conducting qualitative interviews so that they may be well aware of certain pitfalls of asking about ART adherence.

During the training we mainly focused on qualitative interviewing techniques and concepts important to obtaining the highest quality possible information in dealing with medication adherence. This included addressing topics like leading the interviewees or introducing bias into their responses by the way the ask questions and probe. Because many of the interview questions were open-ended or semi-structured, and had many probes, the interview process was a key focus. This was especially important in working with a topic, such as medication adherence, where patients will often want to tell you what you think you want to hear. Also, working with children and getting them to open up can be particularly challenging, so communicating and practicing patience was important for those interviewers who had not worked with children before.

Overall, with strong local input for pre-testing research methods and protocol, an adequately trained study team, and an in-depth understanding of the culture you are working with, such studies are quite feasible and can yield highly valuable information. Communicating with local colleagues and having a research infrastructure already in place made this possible. However there were many other general lessons to be learned in preparation for an international research project.

Lessons Learned in Conducting International Research

Conducting a study in an international setting can be very challenging. Language, cultural, and social barriers can be significant. Also, the resources available in one setting may be completely different than what's available in more familiar settings, such as the USA. If developing a plan to work in a particular resource limited setting, one should take the time to

perform significant research about the place and its people in order to develop a study which is both feasible and valuable for the local population.

Language was the most significant barrier for my participation in international research and should be a primary consideration when working in a foreign setting. Communication is key, and if you cannot communicate effectively it will be impossible to conduct research efficiently. One must successfully communicate with both the study staff and research participants. Fluency in the native language is highly recommended. Though not fully fluent in French, with some effort I felt I was able to engage with my colleagues, communicate each other's needs, and facilitate the research project as successfully as possible. This however took much effort and the availability of an English-French translator. It is also possible the research subjects will speak different languages. In many settings there can be a number of indigenous languages, so preparation for a study should take this into account.

Before developing a research plan for a particular setting, one must 'do their homework'. It is important to have an understanding of the environment. Who are the population and what resources will be available? What are the community's needs? Will a particular project really be useful to the people living in the setting? If so, one must approach working in a new setting with respect. For instance, the typical method to go about achieving an objective or accomplishing a task may be different. You cannot expect people to work as you would in your home environment. Deadlines and meeting times may be much more flexible in certain settings, so one must be patient and able to go with the natural flow, or risk alienating foreign colleagues.

My own personal experience found that more advance planning was needed. Ideally, project planning should not be rushed, as many important things can be overlooked. However, in the real world this must be balanced with deadlines and our own personal time constraints. Namely, my planning issues dealt with budgeting and scheduling, which needed more work before beginning the implementation phase of the project itself and traveling to Kinshasa.

Some unexpected issues were likely unavoidable. However, seemingly basic supplies in this particular setting were quite expensive and fitting the project into my budget was difficult. This may have been better researched before traveling to an international setting. Also, Ethics Committee meetings were not as regular or standardized as with my experiences in the USA, so this process took much longer than anticipated and the project was delayed. Time can run much slower in these settings and expect that less can be accomplished in a given time frame when working in an unfamiliar setting.

These experiences have helped me to better understand how to go about research in a resource limited setting and what type of future expectations I should have when moving forward with future research. Overall, implementing research at the UNC-DRC facility and KLL was challenging, but rewarding. The research plan was flexible enough to where it could successfully be implemented. However, without large amounts of determination and patience on my part, and the knowledge and aid of others in Kinshasa, it would not have been possible.

Acknowledgements:

I would like to first and foremost thank my advisors, Frieda Behets and Russell Harris, for giving me the opportunity to do public health research and work in a unique setting such as the DRC, not to mention keeping me on task! I would also like to thank Carol Golin for her help with qualitative methods and working with ART adherence. I would also like to extend my thanks to the UNC-DRC staff in Kinshasa: Bavon Mupenda, Kash Mwandagalirwa, and Xavier Mbiyi. Also, with the staff at KLL Pediatric Hospital, this would not have been possible: Dr. Faustin Kitetela, Dr. Jean Lusiana, Delphine Kizungu, and Alice Tabala. I would also like to thank Lisa Parker for her help in the training of the research staff.

REFERENCES

1. Joint United Nations Program on HIV/AIDS, 2008. Children and AIDS second stocktaking report Available at:
http://data.unaids.org/pub/Report/2008/childrenandaidssecondstocktakingreport_en.pdf.
Accessed February 24th, 2009.
2. Joint United Nations Program on HIV/AIDS, World Health Organization. AIDS epidemic update: December 2007. Geneva:2007.
3. Sutcliffe CG, van Dijk JH, Bolton C, Persaud D, Moss WJ. Effectiveness of antiretroviral therapy among HIV-infected children in sub-saharan africa. *Lancet Infect Dis*. 2008;8:477-489.
4. Lawn SD, Myer L, Bekker LG, Wood R. CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-saharan africa. *BMC Infect Dis*. 2006;6:59.
5. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1-infected children in abidjan, cote d'ivoire. *AIDS*. 2004;18:1905-1913.
6. Callens SF, Shabani N, Lusiana J, et al. Mortality and associated factors after initiation of pediatric antiretroviral treatment in the democratic republic of the congo. *Pediatr Infect Dis J*. 2009;28:35-40.
7. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet*. 2002;360:119-129.

8. World Health Organization.

Antiretroviral therapy for HIV infection in infants and children: Towards universal access.

Geneva: WHO; 2006.

9. Bikaako-Kajura W, Luyirika E, Purcell DW, et al. Disclosure of HIV status and adherence to daily drug regimens among HIV-infected children in Uganda. *AIDS Behav.* 2006;10:S85-93.

10. Paterson D, Swindells S, Mohr J, et al.

How much adherence is enough? A prospective study of adherence to protease inhibitor therapy using MEMSCaps .

11. Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *AIDS.* 2000;14:357-366.

12. African Network for the Care of Children Affected by AIDS. *Handbook on Paediatric AIDS in Africa.* Kampala, Uganda: USAID Development Experience Clearinghouse; 2004.

13. Maggiolo F, Airoidi M, Kleinloog HD, et al. Effect of adherence to HAART on virologic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-treated patients. *HIV Clin Trials.* 2007;8:282-292.

14. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS.* 2001;15:1181-1183.

15. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. Is there a baseline CD4 cell count that precludes a survival response to modern antiretroviral therapy? *AIDS.* 2003;17:711-720.

16. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. *Pediatr Infect Dis J.* 2008;27:686-691.
17. Levine AJ, Hinkin CH, Marion S, et al. Adherence to antiretroviral medications in HIV: Differences in data collected via self-report and electronic monitoring. *Health Psychol.* 2006;25:329-335.
18. Miller LG, Liu H, Hays RD, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? *J Gen Intern Med.* 2002;17:1-11.
19. Muller AD, Bode S, Myer L, Roux P, von Steinbuchel N. Electronic measurement of adherence to pediatric antiretroviral therapy in south africa. *Pediatr Infect Dis J.* 2008;27:257-262.
20. Davies MA, Boule A, Fakir T, Nuttall J, Eley B. Adherence to antiretroviral therapy in young children in cape town, south africa, measured by medication return and caregiver self-report: A prospective cohort study. *BMC Pediatr.* 2008;8:34.
21. Vaz L, Corneli A, Dulyx J, et al. The process of HIV status disclosure to HIV-positive youth in kinshasa, democratic republic of the congo. *AIDS Care.* 2008;20:842-852.
22. Sankar A, Golin C, Simoni JM, Luborsky M, Pearson C. How qualitative methods contribute to understanding combination antiretroviral therapy adherence. *J Acquir Immune Defic Syndr.* 2006;43 Suppl 1:S54-68.

23. Chalker J, Andualet T, Minzi O, et al. Monitoring adherence and defaulting for antiretroviral therapy in 5 east african countries: An urgent need for standards. *J Int Assoc Physicians AIDS Care (Chic Ill)*. 2008;7:193-199.
24. Puigventos F, Riera M, Delibes C, Penaranda M, de la Fuente L, Boronat A. Adherence to antiretroviral drug therapy. A systematic review. *Med Clin (Barc)*. 2002;119:130-137.
25. World Bank Website, 2009. World bank country classification Available at: <http://web.worldbank.org>. Accessed February 27th, 2009.
26. Polisset J, Ametonou F, Arrive E, Aho A, Perez F. Correlates of adherence to antiretroviral therapy in HIV-infected children in lome, togo, west africa. *AIDS Behav*. 2009;13:23-32.
27. Adamian MS, Golin CE, Shain LS, DeVellis B. Brief motivational interviewing to improve adherence to antiretroviral therapy: Development and qualitative pilot assessment of an intervention. *AIDS Patient Care STDS*. 2004;18:229-238.
28. Ware NC, Wyatt MA, Bangsberg DR. Examining theoretic models of adherence for validity in resource-limited settings. A heuristic approach. *J Acquir Immune Defic Syndr*. 2006;43 Suppl 1:S18-22.
29. Mills EJ, Nachega JB, Bangsberg DR, et al. Adherence to HAART: A systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med*. 2006;3:e438.

30. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: A qualitative systematic review with recommendations for research and clinical management. *Pediatrics*. 2007;119:e1371-83.
31. Hammami N, Nostlinger C, Hoeree T, Lefevre P, Jonckheer T, Kolsteren P. Integrating adherence to highly active antiretroviral therapy into children's daily lives: A qualitative study. *Pediatrics*. 2004;114:e591-7.
32. Merzel C, Vandevanter N, Irvine M. Adherence to antiretroviral therapy among older children and adolescents with HIV: A qualitative study of psychosocial contexts. *AIDS Patient Care STDS*. 2008;22:977-987.
33. Wrubel J, Moskowitz JT, Richards TA, Prakke H, Acree M, Folkman S. Pediatric adherence: Perspectives of mothers of children with HIV. *Soc Sci Med*. 2005;61:2423-2433.
34. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2000;19:1148-1153.
35. Simoni JM, Amico KR, Pearson CR, Malow R. Strategies for promoting adherence to antiretroviral therapy: A review of the literature. *Curr Infect Dis Rep*. 2008;10:515-521.
36. Clark JP. How to peer review a qualitative manuscript. 2nd ed. London: BMJ Books; 2003:219-235.
37. Patton MQ. *Qualitative Research and Evaluation Methods*. 3rd ed. Thousand Oaks, CA: Sage Publications; 2001.

38. Abadia-Barrero CE, Castro A. Experiences of stigma and access to HAART in children and adolescents living with HIV/AIDS in brazil. *Soc Sci Med.* 2006;62:1219-1228.
39. Ellis AE, Gogel RP, Roman BR, Watson JB, Indyk D, Rosenberg G. The STARK study: A cross-sectional study of adherence to short-term drug regimens in urban kenya. *Soc Work Health Care.* 2006;42:237-250.
40. Makoae MG, Jubber K. Confidentiality or continuity? family caregivers' experiences with care for HIV/AIDS patients in home-based care in lesotho. *SAHARA J.* 2008;5:36-46.
41. Joint United Nations Program on HIV/AIDS, 2008. Epidemiological fact sheet on HIV and AIDS: Democratic republic of the congo. Available at:
http://www.unaids.org/en/CountryResponses/Countries/democratic_republic_of_the_congo.asp. Accessed April 15th, 2009.
42. Coghlan B, Brennan RJ, Ngoy P, et al. Mortality in the democratic republic of congo: A nationwide survey. *Lancet.* 2006;367:44-51.
43. Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity of HIV-1 in kinshasa by 1960. *Nature.* 2008;455:661-664.
44. World Health Organization. Democratic republic of the congo data, 2005. Available at:
http://www.who.int/hiv/HIVCP_COD.pdf. Accessed April 15th, 2009.
45. Behets, F., Edmonds, E. Evaluation of SARA ARV adherence: Unpublished data from the kalembe lembe pediatric hospital in kinshasa, DRC. 2009.

46. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2007;46:187-193.

47. Roura M, Busza J, Wringe A, Mbata D, Urassa M, Zaba B. Barriers to sustaining antiretroviral treatment in kisesa, tanzania: A follow-up study to understand attrition from the antiretroviral program. *AIDS Patient Care STDS.* 2009;23:203-210.

Addendum I: Research Plan Interview Script

Participant Study ID _____
SARA ID _____

Date of Interview ____/____/____ (dd/mm/yyyy)
Time Interview Started ____h ____m
Time Interview Ended ____h ____m
Name of interviewer _____

Introduction Script for Adults:

Hello. My name is _____ and I work with a research team at the Kalembe Lembe Hospital. Thank you for taking the time to speak with me about your experiences in providing HIV medicines to the child. I am very interested in learning more about what it is like to care for children who take these kinds of medicines.

(For those with children 8-17 Years of Age. If only have children < 8 years of age, please skip to next paragraph)

With your permission, I would also be interested in speaking with the child about his/her thoughts on taking medicine. I believe this will give helpful information about what it is really like to take these medicines. If he/she have not been told of the illness I will completely respect that and will not refer to HIV in any direct or indirect way. I will ONLY refer to HIV medicines (sometimes called ART) as 'medication', 'medicine' 'pills', 'vitamins' or whatever you would prefer. With your permission, I would like to ask him or her to participate by answering these questions. If you would prefer that he/she not to, that also is acceptable and will not affect your interview.

Before I continue, please take a look over the consent forms. I will need your signed permission to continue with your interview and your signed permission to interview the child. These forms describe in-detail the purpose of the study, as well as the risks and benefits of participating in this study. If you cannot read or if you would prefer, I will read them out loud to you. Please make sure you understand these forms. I can help you if you have any questions or do not understand any part of the forms.

(After consent is signed)

I realize that the HIV medication regimens are complicated and can be very hard for some children to take. It can also be common to miss scheduled doses and many caregivers like you have told me they worry about how hard it is to always give the HIV medicines to their child on schedule. I am very interested in hearing *your opinion* on this topic. There is no right or wrong answer. Please remember everything you say will be kept private and confidential. I will not reveal anything that you tell me to any of the doctors or nurses or other staff at the clinic or to anyone else. As the consent forms mentioned, I will give a code to this interview so that no information that can identify you (like your name or birth date or address) can be linked to anything you say here. What you have to say is very important to me, but you do not have to

answer any question that makes you feel uncomfortable. If you do not wish to answer a question, let me know and I will move on to the next question.

Before I begin the interview, do you have any questions for me?

Also, would you like a snack or a drink at this time? There will be a short break during the interview for another snack, if you like.

First I would like to ask you some questions about you, your household, and your relationship with the child. Then I will move on to questions about the child's medication.

I. Background Information (To be asked of the adults only)

1. Please tell me your age at your last birthday ____ (years)

2a. Have you ever attended school? Yes.....0 No.....1 Unknown.....2

(If 2a is answered as yes)

b. What grade did you complete? _____

3. Please tell me your exact relation to the child

Mother.....0	Uncle.....5
Father.....1	Grandmother..... 6
Sister.....2	Grandfather..... 7
Brother.....3	Non-relative.....8
Aunt..... 4	Other Relative.....9
	Unknown.....88

If Other Relative please specify or General Comments: _____

4. If not a relative, how long have you known the child? ____ (months, years) N/A

(Can skip if caregiver is mother)

5. How would you rate the condition of the child's health at this time? (please circle one)

Very poor..... 0	Quite Good.....3
Poor..... 1	Excellent 4
Moderate..... 2	Don't know 5

6. a. How old is the child? _____ (months or years)

b. What sex is the child? 0.....Male 1.....Female

c. What year in school is the child, or if not in school, what level did they complete? _____

7a. Would you say that you are the primary person who provides care for the child?

Yes.....0 No.....1 Don't know.....88

7b. Please tell me who is the primary person who cares for the child (if not you) or other people who provide care for the child *(May circle more than one)*

Mother.....0	Uncle.....5
Father.....1	Grandmother..... 6
Sister.....2	Grandfather..... 7
Brother.....3	Non-relative.....8
Aunt..... 4	Other Relative.....9

Unknown.....88

If Other Relative please specify or General Comments: _____

8a. Has anyone disclosed the HIV status to the Child?

Yes.....0 (see → 8b) No.....1 Unknown.....2

8b. If yes, what relationship to the child did the person who told them about their HIV status have?

9a. Would you be willing to tell me if you, or anyone else in the home, besides the child, are living with HIV?

Yes.....0 (see → 9b) No.....1

9b. Please list the relation(s) to the child of those people in the home who are living with HIV

II. Qualitative Interview with Adult Caregivers Script

Q1. Please tell me about the role you play in this child's life.

Probes:

- 1) Tell me about times that you spend with the child during a typical day
 - How would you describe the amount of time you spend with the child in general?
 - How much time per day do you spend with each other?
 - How many days out of the week do you generally see the child?
- 2) What kinds of things do you do *for* this child?
- 3) What kinds of things do you do *with* this child?

Q2. Describe to me how the child gets and takes his/her medicines each day.

Probes:

- 1) Tell me about your role in providing the child's medication
 - How often are you present when the child takes his/her medications?
- 2) Tell me about other people who provide the child with medication
 - Will you describe the role of other people who help provide medication?
- 3) Tell me about the child's role in taking his/her medicines on his/her own
- 4) Describe to me how you, or other caregivers, know the child has taken the medication
 - How do you know if they have actually swallowed it?

Q3a. (If child's HIV status is revealed to them as per Part I, Question 7 answered yes)

Please describe the situation when the child was told that he/she has HIV

Probes:

- 1) Tell me why you, or the person who told the child, felt that he/she needed to know at that point
- 2) Describe the child's reaction to finding out that he/she has HIV
- 3) Describe how the child feels about having HIV, at the present time
- 4) How does the child cope with living with HIV at the present time?

Q3b. (If child's HIV status is not revealed to them as per Part I, Question 7 answered *no*)

Please tell me about why you feel the child should not know they have HIV at this point in time

Probes

- 1) What do you tell the child when they ask about the purpose of these medications?
- 2) What does your child suspect about his/her medications?
 - Tell me about things he/she has said about his/her medications
 - Do you think that he/she suspects that he/she has HIV?
- 3) Please describe to me situations in which the child has questioned these medications
 - What prompted the child to ask questions?
 - How did you or others respond when this happened?
- 4) Tell me about any plans you have to reveal at some time to the child that he/she has HIV
 - Why do you feel it will be appropriate then? (If have plans to tell at some point).

Q4. Describe what you believe the HIV medication does for the child

Probes:

- 1) How do you think the HIV medication is helping the child?
 - How was the child before the medications?
- 2) How do you think the HIV medication is hurting the child?
 - Tell me about bad things that have happened because of the medication
- 3) What are your motivations for making sure the child gets their medication?

Q5. Tell me how HIV/AIDS has affected your child

Probes:

- 1) How do you think their life is different with HIV/AIDS compared with children who do not have HIV/AIDS?
- 2) What do you believe happens to children with HIV/AIDS?

Q6. What does being 'adherent' to HIV medications mean to you?

(Please ask all of these)

- a. What does following the doctor's recommendations mean to you?
- b. What does missing a dose mean to you?
- c. What happens when the child misses a dose?
 - What do you think about the effects of missing one dose on the child's health?
 - How does the child make-up for a missed dose, if at all?
- d. What does taking the medicine "on time" mean to you?
 - How is the timing of taking the medicine important, if at all?
 - How do you and the child plan the timing of his/her medications?
 - Does he/she take them at the same time every day?

Q7a. Please give me your opinion of how many doses of HIV medication the child could miss and still be called 'adherent' to medications

LIST: (ask all options; define 'dose' as the full regimen of medications, not just some medications)

- Never misses a dose
- Misses no more than 1 dose per month
- Misses no more than 1 dose per week
- Misses no more than 1 dose per day

Misses no more than 2 doses per day
Other _____

b. How many doses do you think the child could miss in a (day, week) and still have your doctor say the child is doing a good job taking their medications? _____

Q8. Please tell about a typical day for the child and how he/she fits medications into that day.

You are doing great with these questions. We are getting close to half way done. First, would you like another snack or anything else to drink?

Q9. What kinds of things make it hard for the child to take the medication?

Q10. What things about the medications themselves make them difficult to take?

Probes:

1) How do you and the child overcome taking medication that is complicated and must be taken in a specific way?

2) Tell me about any side effects which have made taking medications difficult.

3) How has their taste made them more difficult to take?

Q11 Tell me about anything else you can think of that makes it difficult for your child to take their HIV medicine

Probes:

1) Does medication ever get misplaced or lost?

2) Tell me about when you or your child forgets to take his or her medicine

3) Tell me about times you are unable to make clinic visits or get medication refills

4) Other things?

Q12. Tell me about things which have made it easier for the child to take HIV medication

Probes:

1) How has the support from the family helped?

2) What motivation do you get from thinking that the ART is helping the child to be healthy?

3) How has support from the community helped?

(Questions 13 -17 can serve to explore topics not mentioned in questions 9-12. If the interviewee talks a lot about one particular topic, you do not need to ask it again in the following questions)

Q13. Tell me about how issues with money affect obtaining HIV medications and the child taking their HIV medications, if at all.

Probes:

1) Can you describe other expenses you or your family has because the child has HIV, besides the medications?

2) If you had more money, how would it be easier to provide HIV medications for your child and for him/her to take these medications?

Q14. Please tell me how attitudes about HIV from the people in your community or your society about HIV affects your child being able to take his/her medication

Probes:

- 1) Describe how your community views the HIV/AIDS epidemic
- 2) How does your community feel about children living with HIV?

Q15. How does your family's work schedule or your child's school schedule affect his/her ability to take HIV medication?

Probe:

- 1) How does the absence of parent or family member around make it more difficult for your child to take HIV medication?
- 2) How does going to school make it more difficult for your child to take medications?

Q16. How does the child's living situation make it more difficult to take medications?

Probe:

- 1) Tell me about whether other children who live with this child might make it difficult for the child to take medications
- 2) Tell me about anyone else the child lives with who makes it difficult to take HIV medicine
- 3) How is it difficult for the child to follow a medication schedule in his or her living environment?
- 4) Is there a particular time of day the child has trouble taking medications?

Q17. Tell me about any aspects to your medical care you receive at Kalembe Lembe which make it harder for your child to take medication

Probe:

- 1) Tell me how your relations with the doctors, nurses, and counselors can make it harder for the child to take his/her medications
 - What are bad things about your relations with these people?
 - What are good things about your relations with these people?
- 2) Tell me about your attitudes towards western medicine
 - Does this make it harder for you, the child, or anyone else in the family to take HIV medications?
- 3) How has the medical care you received helped, if at all?
- 4) How do you feel about the instructions you get about these regimens?

Q18a. *(If child's HIV status is revealed to them as per Part I, Question 8 answered yes)*

Since your child has been told he/she has HIV and that is why he/she must take medications, please tell me how you think this helps or hurts your child in taking HIV medications

Probes:

- 1) Is he/she more motivated because of this?
- 2) Because he/she understand it, is he/she more willing?
- 3) Does the child get frustrated taking his/her medication?

Q18b. *(If child's HIV status is not revealed to them as per Part I, Question 8 answered no)*

Since your child has not been told that he/she has HIV and he/she doesn't know the true purpose of his/her medications, please tell me how you think this helps or hurts your child in taking his/her HIV medications

Probes:

- 1) Does he/she have trouble getting motivated to take his/her medication?
- 2) Does he/she ever simply not want to take his/her medications?
- 3) Does the child get frustrated taking his/her medication?

Q19. Tell me about any specific strategies you or the child have used to take medications every day and on time.

Probes:

- 1) Please give me specific examples
 - Have you used alarm clocks?
 - Do you place the pills in a special place?
 - Do you keep a log?
 - Any other special reminders?

Q20. What responsibility do you believe your community (for example family, friends, and neighbors) have in helping the child to take their HIV medication, if any?

Probe

- 1) If none, do you believe the community should play a role?
- 2) If none, what impedes the community from playing a role in helping your child to take medication?

Q21. (Ask if the Section I, question 8 is **yes** AND the caregiver listed him or herself as HIV positive)

Can you please tell me how your experience with HIV has helped your child to cope with his/her illness and to take medications?

We have almost completed the interview. Thank you for your patience in answering these questions. Finally, we would like to specifically ask whether the child has missed any recent doses of HIV medication. I know that most people have trouble taking all of their medication exactly as recommended. Please tell me what you are actually doing. Don't worry about telling me that you don't take all your pills or medicines. I need to know what is really happening, not what you think I want to hear.

Q22. Can you tell me about any doses the child has missed recently?

(Please ask all the following)

- a. Thinking back to yesterday, how many doses of his/her medicines did the child miss yesterday?
- b. How about the day before that? And the day before that?
- c. Specifically, which doses did he/she miss? (For example morning, afternoon, or night)
- d. Because the child takes several different medications, is there one that he/she tends to miss most often?
- e. Has the child missed any doses in the last week? Can you tell me how many?
- d. Has the child missed any doses in the last month? Can you give me an idea of how many?

Thank you very much for answering our questions. I appreciate that you took the time to answer them. This concludes our interview and you are free to go.

III. Qualitative Interview Script for Children who DO know their HIV Status

Hello. My name is _____ and I work with a medical research team at the Kalembe Lembe Hospital. I would like to talk with you today about your experiences in taking

your HIV medicine. I am very interested in learning more about what it is like for you to take this. Would it be ok for me to ask you some questions?

→(If child is 13 years of age or older and assent form is needed).

Let me begin with some information about these questions. They are part of a study run by the clinic, the hospital, and the University of North Carolina, in the United States. Since you are old enough to make decisions for yourself, I would like you to look over a form which gives you some details on the types of information I will be asking about. I will ask that you sign the form in order to give me permission to ask you questions. This form will tell you about the purpose of this study, as well as some risks and benefits of participation this study. If you would prefer, I can read it out loud to you. I can help you if you have any questions or do not understand any part of the forms.

→(If child is younger than 13 years of age and no assent form needed)

Let me begin with some information about these questions. They are part of a study run by the clinic, the hospital, and the University of North Carolina, in the United States. These questions will ask you about your relationship with the person who brought you to clinic today, your thoughts about HIV and the medicine you take for it, as well as things that make it harder or easier to take your medications. This will take between 30 minutes and an hour and a half. Is it ok with you to continue?

(After assent given)

I realize that taking your HIV medicine every day can be really hard. It can also be common to miss scheduled doses. Young people like you have told me that they worry about how hard it is to always take their medicine on schedule. I am very interested in hearing *your opinion* on this topic, so there are no right or wrong answers. Please be reminded that everything you say will be kept private and confidential. I will not tell anything you say to the doctors or nurses or other staff, not even with the person who brought you to clinic, or with other family members or friends. I will give a special code to this interview and no information that can identify you (like your name or birth date) can be linked to anything you say here. You are not required to answer any question you do not feel comfortable with. If you do not wish to answer a question, let me know and I will move on to the next question.

Before I begin the interview, do you have any questions for me?

First I would like to ask you a few questions about yourself.

Q.0 How old are you? _____ (months or years)

What sex is the child (*please make an observation, do not ask unless unsure*)

0.....Male 1.....Female

What year in school are you, or if not in school, what level did you complete? _____

Q1. Can you tell me about your relationship with the person who brought you to clinic today?

Probes:

1) What is their relation to you?

- 2) Tell me about a typical day you spend with this person
 - How much time per day do you spend with each other?
 - How many days out of the week do you see this person?

Q2. Can you describe to me who helps you the most with taking your pills

Probes:

- 1) Do you or someone else have most the responsibility in taking your pills?
- 2) Can you describe all the people who help you take your pills?

Q3. Please tell me about a typical day taking your pills

Probes:

- 1) Can you tell me about your routine?
- 2) How many times do you take pills each day? How many pills each time?

Q4. Can you describe your role in taking your pills?

Probes:

- 1) Does someone else remind you to take pills, or do you remind yourself?
- 2) How do you get your pills every day?
 - Who gives them to you to take?
- 3) Does anyone else besides you check to see if you have taken your pills?
 - If so, how do they check?

Q5. Please tell me what you know about HIV

Probes:

- 1) What have you learned about HIV?
- 2) What have people told you about HIV that you think is wrong?

Q6. Tell me what you remember about finding out that you had HIV

Probes:

- 1) How did you find out?
- 2) How long have you known?
- 3) How did you feel when you were told?
- 4) Are you glad you know?
 - Why or why not?

Q7. Tell me what you think about your HIV medications

Probes:

- 1) What do you believe these pills do for you?
- 2) How do these medications help you?
- 3) How do these medications hurt you?
- 4) Do you trust these medications?
 - Why or why not?
- 5) How long do you think you will have to take these pills?

- 6) Do you like taking your medications?
-Tell me why or why not

You are doing great with these questions. We are about half way done. First, would you like another snack or anything else to drink?

Q8. What kinds of things make it hard for you to take your medication?

Q9. What is it about the medicine themselves that make them harder to take?

Probes:

- 1) Tell me about how side effects make it harder to take your pills
- 2) Tell me about how taste makes it harder to take your pills.
-Are your pills or the liquid hard to swallow?
- 3) Tell me how taking your pills multiple times per day makes it harder.

(Questions 10 -13 can serve as probes to Question 8-9. If the interviewee talks a lot about one particular topic, you do not need to ask it again in the following questions)

Q10. *(If the child goes to school)* Tell me how going to school makes taking your medication harder

Probes:

- 1) What do people at your school think about other kids with HIV?
- 2) How do you try to hide taking your medicine at school?
-Why do you do this?
-Does this make taking your medicine more difficult?

Q11. Tell me about things at home which make it harder to take you medications

Probes:

- 1) Tell me how other people in the home make it harder
- 2) Does having lots of people around make it harder to take?
-It is easier to forget or misplace medications?

Q12. Tell me how your community makes it harder to take your medicine?

Probes:

- 1) Do you think people judge you for having HIV?
-Tell me about that.
- 2) How do people in your community make you feel about having HIV?
-Do people know?
- 3) Do these things make you want to hide taking your pills?
-Why or why not?

Q13. You have mentioned some interesting things about taking your pills. What about for other people your age? Can you think of some things we didn't talk about that make taking HIV medicine harder for other people your age? (Not necessarily you)

Probes:

- 1) Is it easy to forget taking these pills?
-Tell me about that